THE JOURNAL
of the American Medical Association
Published Under the Auspices of the Board of Trustees
VOL. 150, NO. 16 CHICAGO, ILLINOIS DECEMBER 20, 1952
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SOME ASPECTS OF THE LEUKEMIA PROBLEM

THE MINOT LECTURE

Cyrus C. Sturgis, M.D., Ann Arbor, Mich.

George Richards Minot will be remembered for his ability as a teacher and clinician, but of all his contributions to medicine, the introduction of liver in the treatment of pernicious anemia was the greatest. By so doing he provided the means whereby patients with this otherwise inevitably fatal disorder could survive in a good state of health for a normal span of life. For this he was the co-recipient of the Nobel Prize in 1934.

This monumental discovery is an excellent example of how much can be accomplished by a man if he has a comprehensive knowledge of medicine, persistence, abundant enthusiasm, dogged determination, and an inquiring and restless mind. In his thoughts he was constantly casting here and there for the solution of some clinical problem, often, but not always, of a hematological nature. But he did not usually conclude such speculations without putting his thoughts into action. In this he exemplified what Bacon advised when he said, "We have not to imagine or think out, but to discover what nature does." Or, paraphrasing the words which John Hunter said to William Jenner, "Do not limit your inquiry to meditation—try."

This spirit of investigation and the ability to drive incessantly toward a clearly defined objective constituted his greatest assets. He never stopped or became discouraged, nor did he permit any circumstances to deter him from trying to solve a problem that he thought was worth while. Thus came into being one of the greatest advances in the science of hematology of all time, the therapeutic control of pernicious anemia, which heretofore had been a completely unsolved problem.

There are many important aspects of leukemia that merit discussion and require elucidation. I have chosen, however, to confine my remarks to three of them, as follows: the possible increasing incidence of the disease; the etiology of the disorder; and an evaluation of the effectiveness of the more recently introduced methods of treatment as well as some of the older ones.

ETIOLOGY

The generally accepted theory of the cause of leukemia is that certain genetic influences, acting in conjunction with unidentified external factors, transform normal hematological cells into ones that have an unrestrained and purposeless growth. According to Furth,[1] the fundamental change resides in the leukemic cells and consists of an acquired inability of immature leukocytes to respond normally to forces that regulate their proliferation and maturation.

A great majority of clinicians who have had a long experience with the disease, on correlating their impressions of its nature with the many experimental studies that have been made on it, have arrived at two definite conclusions. First, the etiology of leukemia is still uncertain, and second, the balance of evidence at present predominantly favors the neoplastic theory; the latter view serves the clinician best. Additional knowledge, however, may modify the present concept.

The clinical features and the fatal termination are due to (1) the impairment of function of the various body tissues resulting from the characteristic leukemic infiltrations; (2) the development of anemia, usually myelophthisic in nature; (3) lessened resistance to infection due, at least in part, to diminished phagocytic activity; and (4) a hemorrhagic tendency resulting from the destruction of megakaryocytes in the bone marrow and consequently a decrease in the number of circulating blood platelets. Although all of the etiological factors are not known, two important ones have been clearly demonstrated. These are that heredity undoubtedly plays a role and that exposure to the roentgen rays in small doses over long periods increases the possibility that any given person will develop the disease.

Role of Heredity.—It has been shown repeatedly in animals, especially rats and mice, that the susceptibility to experimental leukemia, and the transmission of the spontaneous disease, follow definite genetic laws. This

From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.
Because of space limitations, some of the bibliographic references have been omitted from THE JOURNAL and will appear in the author's reprints.
Read before the Section on Experimental Medicine and Therapeutics at the 101st Annual Session of the American Medical Association, Chicago, June 11, 1952.
1. Furth, J.: Recent Studies on the Etiology and Nature of Leukemia, Blood **6**: 964, 1951.

receives additional support from two clinical sources. One is that the occurrence of two or more cases in the same family cannot be explained on the basis of chance alone, and the other is the demonstration by Videbaek [2] that the incidence of the condition in the blood relatives of patients with leukemia is 17 times as great as in a comparable control group.

The literature with reference to the occurrence of another case of leukemia in blood relatives has been reviewed by Ardashnikov,[3] who lists 31 instances in which this has been noted. One of the most striking such examples was reported in 1951 by Anderson,[4] who observed the disorder in five of eight siblings. The disease occurred in all of the patients between the ages of 5 and 8 years. Three of the patients had lymphatic leukemia, and in two it was regarded as reticuloendotheliosis. Blood studies on the parents and the unaffected siblings revealed no abnormalities. No other blood disorder and only one case of cancer could be elicited in the family history, which included 135 relatives. Nevertheless, it seems highly probable that a genetic factor must have been involved. It is suggested by Anderson that instead of the more popular concept of a dominant gene with a low penetration, one might postulate that in this particular family there was a rare recessive gene with high penetration.

Role of Exposure to X-Rays.—It has long been recognized that the incidence of leukemia in radiologists is significantly higher than the occurrence of the disorder in physicians who are not exposed repeatedly to the roentgen rays. A recent article by March deals with this subject.[5] He shows in a study covering a 20 year period that the condition is observed nine times as frequently in radiologists as in nonradiological physicians. Furthermore, evidence is cited to indicate that the disorder occurs twice as commonly in physicians as a whole as in the general adult male white population. It is emphasized by March that the occupational hazard of roentgenology has not been given sufficient attention and that the standard means of protection are inadequate and difficult to employ in routine work. Although this etiological factor is probably of relatively minor importance from the standpoint of the actual number of cases of the disease for which it is responsible, it is of great significance in that it undoubtedly favors the development of the leukemia state.

POSSIBLY INCREASING INCIDENCE OF LEUKEMIA

Leukemia can no longer be regarded as a rare disease. In 1942 [6] the condition accounted for more deaths in the United States than those due to smallpox, meningococcus meningitis, scarlet fever, poliomyelitis, malaria, typhoid fever, and diphtheria combined. Furthermore, the mortality rate from leukemia is now higher than that due to anemia, whooping cough, dysentery, or alcoholism. About 5,000 deaths occur annually from the disease.[7]

Is the greater number of cases observed more apparent than real? In my opinion, certain obvious factors can account for some but not all of the increase. For example, at present the condition is more frequently recognized because many more complete blood examinations are done than a few years ago. Furthermore, it has been only in recent years that the invaluable procedure of sternal puncture has been commonly employed. The information thus made available accounts for the disease being recognized in many patients with the subleukemic and aleukemic types that otherwise would be overlooked.

The increased incidence of leukemia is present in all age groups. The fact that more persons survive to the age when the disease is prevalent, therefore, does not entirely account for the increased occurrence. This in part is true, however, as some types of leukemia, such as the monocytic variety, are observed most frequently between the ages of 25 and 60 years, and more persons are now surviving to this age.

While there is no convincing proof that incriminates roentgen ray exposure as a cause of the increasing incidence of leukemia, two facts in relation to this possibility must be kept in mind. First, a large percentage of our population is subjected to roentgen ray examinations, especially since the introduction of the most useful procedure of employing microfilms in the detection of pulmonary tuberculosis. Moreover, the roentgen ray is used much more frequently now for other essential diagnostic purposes. Hardly a patient enters a hospital in this country at the present time without being exposed to x-rays once or many times. The great diagnostic value of such examinations cannot be questioned. Undoubtedly information derived from them is life-saving in many instances, and no information now available would indicate positively that the use of such necessary diagnostic procedures should be curtailed.

The second fact that suggests the possible role of x-rays in the increasing incidence of leukemia is the observation, previously discussed, that the disease is nine times more prevalent in roentgenologists than in the population at large.[5] The role of x-rays as a factor in the general increased incidence of leukemia is, however, far from proved. It is difficult to conceive that the effect of isolated exposures, taken of persons for diagnostic purposes, in any way is comparable to the effect of almost constant daily exposure of the roentgenologist over many years.

It is of interest in this connection that in a study of 5,000 Japanese at Hiroshima and a small number at Nagasaki Bugher [8] found that in persons who received effects from the atom bomb leukemia developed 10 to 20 times as frequently as it naturally develops in nonexposed populations. Furthermore, those who were directly under the atom bomb blast, where exposure was greatest, were most prone to become leukemic.

TREATMENT OF LEUKEMIA

The following facts concerning therapy appear to have been clearly established: 1. There is no cure for the disease. 2. The palliative results are often excellent, and a patient may be maintained in a practically normal condition for 80 to 90% of the survival period, averaging two to four years, but in exceptional cases it may be much

2. Videbaek, A.: Heredity in Human Leukemia and Its Relation to Cancer, Copenhagen, Denmark, Eljnar Munksgaard Forlay, 1947.
3. Ardashnikov, S. N.: Genetics of Leukaemia in Man, J. Hyg. **37**: 286, 1937.
5. March, H. C.: Leukemia in Radiologists in a 20 Year Period, Am. J. M. Sc. **220**: 282, 1950.
7. Sacks, M. S., and Seeman, I.: A Statistical Study of Mortality from Leukemia, Blood **2**: 1, 1947.

longer. 3. The downward course of any form of leukemia, including the most acute types, may be temporarily reversed by various recently introduced therapeutic measures. 4. When a patient eventually becomes refractory to one form of treatment, benefit may be observed from some other therapeutic agent.[9] 5. When all types of therapy are employed, there may be some prolongation of life, but this is usually for a relatively short interval. 6. The main problem of treatment centers about the nature of the mechanism of complete refractoriness to all forms of treatment, which eventually develops in every patient with the disease.

It is probably not true that patients fail to be benefited by therapy that was previously successful because they are capable of responding to only a certain number of treatments and then develop an immunity to them. This mechanism would be analogous to bacteria becoming immune to certain antibiotic agents. It is now generally believed that this eventual ineffectiveness is associated with the natural course of the disease, that is, the condition progresses to a state resistant to all therapy, regardless of whether prior treatments have or have not been given.

The various treatment agents available for use in patients with leukemia are as follows: (1) blood transfusions; (2) antibiotics and sulfonamides; (3) arsenic; (4) total body and regional roentgen ray irradiation; (5) radioactive phosphorus (P^{32}); (6) urethane (ethyl carbamate); (7) the nitrogen mustard group, including HN_2, SK-136, and triethylene melamine (TEM); (8) folic acid antagonists (aminopterin and others); (9) corticotropin (ACTH) and cortisone; and (10) splenectomy.

Use of Blood Transfusions and Methods of Combating Infection.—There is general agreement concerning the use of blood transfusions and methods of combating infection in this disease. It is desirable that the hemoglobin be maintained at a level of 11 gm. (70%) or higher, if this can be accomplished by means of various forms of treatment and repeated blood transfusions. This level is arbitrarily chosen because a hemoglobin percentage lower than this is usually associated with the general symptoms of an anemia. By the proper use of transfusions, the patient can be kept free from such symptoms for long periods of time and hence made more comfortable. Furthermore, it is possible that by maintaining the hemoglobin at a level of 11 gm. per 100 cc. or higher, the resistance to infection is improved.

Exchange or substitution blood transfusions in which a considerable amount of blood is removed from a patient with acute leukemia and replaced by blood from a normal donor have received a limited trial. Reports on the value of this procedure [10] have suggested that effects somewhat superior to those of ordinary blood transfusions given at frequent intervals may be obtained. Further observations are desirable, however, in order to evaluate it more completely. As the administration of an exchange transfusion is a complicated procedure, and as the results are not strikingly better than ordinary transfusions, it cannot be recommended as a routine form of treatment at present.

If infection appears in the mouth or other mucous surfaces, or elsewhere, antibiotic therapy is indicated. In my experience this treatment is superior to the use of sulfonamides. For acute infections I usually give 400,000 units of penicillin intramuscularly twice daily, with or without the additional use of aureomycin orally in doses of 0.25 gm. every six hours. This combination is usually the most effective in the control of oral infections. It may be necessary, however, in some patients to add other antibiotics such as terramycin or streptomycin.

Arsenic as a Therapeutic Agent.—The earliest treatment of leukemia that produced favorable effects was arsenic. When given in the form of Fowler's solution (potassium arsenite) to tolerance, it sometimes produces satisfactory results, especially in patients with chronic granulocytic leukemia. With so many other different methods of treatment now available, however, it is hardly worth while to employ arsenic. The drug acts as a protoplasmic poison, which probably injures leukemic cells by interfering with cellular oxidation.

The initial dose of Fowler's solution should be 4 to 5 minims (0.25 to 0.3 cc.) orally three times daily, gradually increasing to the most effective dosage, which may be as much as a total of 40 minims daily. The medication should be given after meals, well diluted with fruit juice. Nausea and vomiting and diarrhea may be the earliest toxic manifestations, and occasionally a brownish pigmentation of the skin may result. In order to avoid severe untoward effects, the drug should be given in a 21 day cycle of increasing doses followed by 21 days of rest.

Urethane.—Urethane may be used in the early stages of chronic granulocytic leukemia in initial doses of 0.3 gm. three times daily of enteric coated tablets. The total dose should be increased each day by 0.3 gm. until a maximum of 3.0 gm. is reached. In many patients this has a beneficial effect, but the results are inferior to those following irradiation. Furthermore, in my experience, when an effective dose has been reached, the patient often complains of persistent and annoying anorexia, nausea and vomiting, and consequently administration of the drug must be discontinued.

A beneficial effect is usually observed within three weeks, as evidenced by a decrease in the total white blood cell count and a partial or complete relief of the patient's symptoms. When a satisfactory remission has been attained, then a maintenance dose of 1.0 to 1.5 gm. daily may be given. Leukocyte counts should be done at intervals to control the treatment. The drug may be used in conjunction with x-ray therapy in an attempt to lengthen the intervals between the application of roentgen ray therapy. It is of no value in the acute leukemias or the acute exacerbations of chronic leukemia.

Triethylene Melamine.—The use of triethylene melamine should be considered in all patients with chronic granulocytic leukemia who have become refractory to irradiation.[11] This preparation should be given preferably by mouth in doses of 2.5 to 5 mg. every other day for a total of 12 to 25 mg. and then stopped. The total dose may be repeated in 14 days if the leukocyte count is 5,000 per cubic millimeter or higher and no severe toxic symptoms are present. The optimum maintenance dose

9. Pillers, E. M. K.; Burchenal, J. H.; Eliel, L. P., and Pearson, O. H.: Resistance to Corticotropin, Cortisone, and Folic Acid Antagonists in Leukemia, J. A. M. A. **148**: 987 (March 22) 1952.

has not yet been determined, but the drug may be given in amounts of 2.5 to 5 mg. every two weeks, and increased or decreased according to the presence or absence of toxic manifestations and the control of symptoms.

Triethylene melamine, introduced into clinical medicine by Rhoads and his associates in 1950,[12] is a complex organic compound similar in its therapeutic effects to HN_2. It can be given orally but is about two times as toxic as HN_2. Good temporary palliative results are obtained with triethylene melamine in Hodgkin's disease and chronic myelogenous and lymphatic leukemia, but less frequently in lymphosarcoma and reticulum cell sarcoma, and not at all in acute leukemia. Its extreme toxicity, however, prevents its widespread use at present. The intravenous dose is about one-third that of the oral dose. Publications in 1951 and 1952 dealing with its clinical use are those of Karnofsky and associates,[13] Wright and his associates,[14] Rundles and Barton,[15] and Silverberg and Dameshek.[16]

Nitrogen Mustard.—Nitrogen mustard (HN_2), when given to an adult in doses of 6 mg. intravenously every other day for four doses, and repeated in a month if necessary, may be of benefit in chronic granulocytic leukemia. It is, however, not recommended as the most effective treatment in this condition.

Corticotropin and Cortisone.—In the terminal stages of chronic granulocytic leukemia, when irradiation, urethane and triethylene melamine are no longer effective, corticotropin or cortisone deserves a trial. In many patients there may be a certain amount of euphoria and temporary relief of symptoms, and in about 10% of the adults even more beneficial effects will appear. The younger the patient, the greater the chances of improvement. In adults, cortisone may be given orally in doses of 75 mg. every six hours, for two to three weeks, and then reduced gradually over a four day interval to 75 mg. daily. Corticotropin is given subcutaneously in a dosage of 25 mg. every six hours for the same length of time, and then reduced to 25 mg. daily.

Splenectomy in Leukemia.—In rare instances, probably in less than 5% of all patients with leukemia, the possibility that worthwhile temporary improvement may follow splenectomy makes a consideration of this operation necessary. The value of this therapeutic measure has recently been reviewed by Fisher, Welch and Dameshek [17] and the literature dealing with the subject summarized. They conclude that splenectomy in leukemia and lymphosarcoma should be properly confined to a small number of especially selected cases.

Only two possible indications for this operation merited consideration. One was a grossly enlarged spleen with constantly associated severe pain and distress that had not yielded to roentgen therapy or other antileukemia measures. This indication, in my opinion, is no longer valid, because medical measures usually control such complaints. If not, the good to be accomplished by surgery is scarcely worth the risk and discomfort of such an operation. The other indication is the presence of a hemolytic anemia instead of the usual myelophthisic type. The former is observed in less than 5% of all patients with the disorder. Its presence should be suspected when blood transfusions must be repeated at frequent intervals, when there is a slight icteric tint, increased blood bilirubin, evidence of hyperplasia of the red-blood-cell-forming elements in the bone marrow, and an increased reticulocyte count, and the presence of nucleated red blood cells in the circulating blood. Such an anemia is normocytic or slightly macrocytic and normochromic in type.

If the anemia is thought to be hemolytic in nature, the bone marrow is found to contain nucleated red blood cells and megakaryocytes, and the spleen is enlarged, which, of course, it is in almost all types of leukemia, the possibility that the syndrome of "hypersplenism" is present must be taken into consideration. Furthermore, temporary relief following splenectomy is reasonably certain. Before the spleen is removed, however, in all cases a trial of corticotropin or cortisone therapy should be given for 10 to 12 days. If this fails, then the possibility of splenectomy must be considered. Its value in the management of such patients, however, is questionable in my opinion.

Folic Acid Antagonists.—Since the folic acid antagonists were first used, a sufficient number of patients have been treated to permit definite conclusions, as follows: 1. These substances, of which "aminopterin" (4-aminopteroylglutamic acid) and amethopterin (4-amino-N^{10}-pteroylglutamic acid) are the most commonly employed, are of value only in the treatment of acute leukemia. 2. Striking temporary benefit results in about 50% of children with acute leukemia, and important improvement in a total of about two-thirds of the patients. 3. Although Farber [18] concludes that they are effective in only about 13% of the adults with acute leukemia, our results are better, as worthwhile relief has been observed in about one-third of such patients.

It is clearly demonstrated, therefore, that temporary benefit follows the use of these drugs in a relatively high percentage of children, but in a smaller group of adults. "Aminopterin" is given cautiously in daily doses of 0.5 to 1.0 mg. by mouth to children. In adults the oral dose is 2 mg. daily for a few days followed by a maintenance dose of 1 mg. or less daily. Evidence of clinical and hematological improvement will appear within two to three weeks. In some instances, when the patient is moribund, signs of a return toward normal may be apparent within a few days. The salutary effect may vary from an estimated 50% return to normal to a complete temporary recovery, judging from the amelioration of symptoms and changes in the circulating blood and bone marrow. In the opinion of Farber,[18] the survival time is prolonged, and as evidence of this he cites two patients in apparent good health 26 and 29 months after the proved onset of acute leukemia.

While the results attained by the folic acid antagonists indicate that the condition can be reversed temporarily in a substantial group of patients, the treatment has its drawbacks. In the first place, the drugs are all toxic, and the margin between the therapeutic and toxic dose is not great. Experience has shown that the untoward effects are of two main types, namely (1) injury to the bone marrow with reduction in the circulating erythrocytes,

17. Fisher, J. H.; Welch, C. S., and Dameshek, W.: Splenectomy in Leukemia and Leukosarcoma, New England J. Med. **246**: 477, 1952.

leukocytes, and blood platelets, and (2) a destructive action on the epithelium of the intestinal tract. If a patient under treatment, therefore, has frequent blood examinations and the treatment is guided by changes chiefly in the platelets and white blood cells, and attention is directed toward the developments of a sore mouth, the more serious toxic effects may be avoided. Ulceration of the mucous membrane of the oral cavity is one of the earliest untoward results and is an indication for prompt omission of the drug; to continue the medication would be running the risk of causing hemorrhage from the bowel.

TREATMENT OF DIFFERENT TYPES OF LEUKEMIA

Treatment of Chronic Granulocytic Leukemia.—In my opinion there are two indications for the treatment of chronic granulocytic leukemia with therapeutic agents that are directed toward the disease processes proper. They are (1) evidence of progression of the condition such as a consistently rising leukocyte count, persistent symptoms referred to the splenomegaly, anemia, hemorrhagic manifestations, fever, increasing fatigue, and weight loss and (2) the presence of a leukocyte count greater than 40,000 per cubic millimeter.

In patients with this form of leukemia, I prefer to use radioactive phosphorus (P^{32}) in an initial dose of 5 mc. given intravenously. After six weeks, if the total white blood cell count is not appreciably reduced, a second but somewhat smaller dose (3 to 4 mc.) should be administered. If provisions are available for the handling of this isotope, it is the most convenient and efficient form of therapy to use in this condition. It can be given on an outpatient basis, as in my experience there has never been any more reaction to such therapy than to the administration of a similar quantity of normal saline solution. Nor is the patient thus treated a hazard to others with whom he comes in contact as beta rays only are emitted and they travel no farther than a few millimeters.

If radioactive phosphorus is not available, then I employ total body irradiation in small doses, repeated every other day, until the white blood cell count is in the vicinity of 20,000 per cubic millimeter. Local roentgen therapy is given in such patients only when there is gross splenic enlargement or pain over the spleen, which is usually associated with a perisplenitis. In my opinion, until recent years, two mistakes have been made in the roentgen therapy of this type of chronic leukemia; either the dosage has been excessive with a resultant increase in the undernutrition and anemia, or the patient has been permitted to relapse too far before treatment is given.

By irradiation, a patient with chronic granulocytic leukemia may be kept in a condition that varies from one of apparent health to a reasonably satisfactory state, for a variable period of time, usually between 3 to 3.5 years. It is reported by Lawrence and his associates,[17a] however, that in treating 129 patients with chronic granulocytic leukemia with P^{32} alone or in combination with x-ray irradiation, the average length of life was 3.7 years with 21 of the patients still alive.

There are several other therapeutic agents, as previously mentioned, which are of some value in the treatment of this form of leukemia. They are urethane, triethylene melamine, and the nitrogen mustards.

Treatment of Chronic Lymphatic Leukemia.—In general, the same principles of treatment apply to chronic lymphatic leukemia as they do to the chronic granulocytic variety, with a few important exceptions. Irradiation is the treatment of choice, and while P^{32} in the dosage used for the granulocytic type may produce good results, it is not as uniformly satisfactory as in the latter variety. For this reason, it is probably preferable to say that the recommended initial treatment should be localized roentgen therapy, with the same indications and contraindications as in chronic granulocytic leukemia.

Likewise, urethane and the nitrogen mustards are of value, but are also less effective than in the chronic granulocytic type. It is probable that triethylene melamine is as useful as in the granulocytic variety. This form of treatment may be given a trial, therefore, when the patient is no longer benefited with irradiation therapy.

Treatment of Acute Leukemia.—Acute leukemia usually has a fulminating course, terminating fatally within a few weeks to six months. In a group of 172 cases of acute leukemia observed by Southam and his associates [19] 50% were dead in 17 weeks, and 90% by 36 weeks. In about 8 to 10% of the patients, however, there may be a single brief partial or complete spontaneous remission.

It was reported in 1950 by Bierman and his associates [20] that children with acute or chronic lymphogenous leukemia survive for an average of 5.6 months from the onset of symptoms when untreated; for 5.8 months when treated with blood transfusions, antibiotic therapy and irradiation; for 6 months when receiving blood transfusions but no penicillin or sulfonamide therapy; and for 8.9 months when blood transfusions and antibiotics are used. These observations indicate that irradiation alone is of no value in prolonging life and that the optimum, but only slightly effective, therapy before the introduction of corticotropin and cortisone and folic acid antagonists, was limited to antibiotics and blood transfusions.

Following the studies of Dougherty and White [21] in 1943 showing that corticotropin will cause a decrease of lymphatic tissue in animals, it was suggested by Pearson and associates [22] and Farber [23] that these substances might be of benefit in treating patients with acute leukemia. Since then it has been demonstrated that about two-thirds of the children with this disorder will show clinical improvement and about one-third favorable changes in the blood, following the daily use of 50 mg. of corticotropin or 150 mg. of cortisone. The remissions are always temporary, usually being of 4 to 8 weeks' duration, but some have persisted for as long as 30 weeks. When a relapse does occur, a second remission, and sometimes as many as four, have been induced in the same patient. The results of this form of treatment in

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17*a*. Lawrence, J. H.; Dobson, R. L.; Low-Beer, B. V. A., and Brown, B. R.: Chronic Myelogenous Leukemia; Study of 129 Cases in Which Treatment Was with Radioactive Phosphorus, J. A. M. A. **136**: 672 (March 6) 1948.

19. Southam, C. M.; Craver, L. F.; Dargeon, H. W., and Burchenal, J. H.: A Study of the Natural History of Acute Leukemia with Special Reference to the Duration of the Disease and the Occurrence of Remissions, Cancer **4**: 39, 1951.

22. Pearson, O. H.; Eliel, L. P., and Talbot, T. R., Jr.: Use of ACTH and Cortisone in Neoplastic Disease, Bull. New York Acad. Med. **26**: 235, 1950.

23. Farber, S., and others: The Effect of ACTH in Acute Leukemia in Childhood, Proc. First Clinical ACTH Conference, Philadelphia, The Blakiston Co., 1950, p. 328.

adults, however, is much less promising, as improvement is produced in less than 10% of the patients. All patients thus treated should receive a low sodium diet.

It is generally accepted that the beneficial effects resulting from corticotropin or cortisone are inferior to those due to the folic acid antagonists. Owing to the short periods of remission induced by these hormones, it is recommended by Farber [18] that they be used only when the patient is extremely ill and a rapid remission is desired. Once it has been produced, then the hormone therapy should be discontinued and one of the folic acid antagonists given. In some instances, however, when the patient with acute leukemia no longer responds to folic acid antagonists, varying degrees of improvement may follow the use of corticotropin or cortisone.

Treatment of Other Types of Leukemia.—The treatment of choice in patients with lymphosarcoma and reticulum cell sarcoma is x-ray irradiation with the knowledge that some benefit can also be derived from the use of the nitrogen mustards. In both conditions improvement may follow the use of triethylene melamine. In chloroma, the most satisfactory therapy is x-ray irradiation. Patients with multiple myeloma usually derive the most benefit from roentgen therapy, which is of great value in the relief of pain associated with bone involvement. Good results have followed the use of urethane and corticotropin and cortisone, and they should be given a trial when irradiation is no longer effective.

Patients with monocytic leukemia, either of the myelomonocytic or the histiomonocytic variety, frequently present a problem in therapy as they often do not respond favorably to any form of treatment. In many instances this is because they are acute or subacute in nature and often of the subleukemic variety. Unless there are definite contraindications, probably the best form of treatment is irradiation with the roentgen rays. This is frequently contraindicated, however, on account of the low level of the leukocyte count or because the disorder is of the acute or subacute variety. Urethane and corticotropin or cortisone may be given a trial, but the results are usually not satisfactory. In all of the above types of leukemia, blood transfusions and antibiotic therapy are often of benefit when the usual indications are present.

SUMMARY

In general, it may be said that irradiation, either in the form of radioactive phosphorus or total body irradiation, is the treatment of choice in patients with chronic granulocytic leukemia. In chronic lymphatic leukemia, localized roentgen irradiation is probably the most satisfactory form of therapy, although radioactive phosphorus can be used. Nitrogen mustard is only moderately effective in leukemia but is of great value in Hodgkin's disease. Folic acid antagonists are indicated in acute leukemia, as is corticotropin and cortisone; they produce more satisfactory results in children, however, than in adults. Multiple myeloma and chronic granulocytic leukemia are benefited by urethane, corticotropin (ACTH) and cortisone, but x-ray therapy is a superior form of treatment. Definitely favorable effects are produced by triethylene melamine in some patients with chronic granulocytic and chronic lymphatic leukemia, in Hodgkin's disease, and a fair proportion of patients with lymphosarcoma.

1313 E. Ann St.

DIAGNOSIS AND TREATMENT OF ACQUIRED HEMOLYTIC ANEMIA

Milton S. Sacks, M.D., Joseph B. Workman, M.D.
and
Elsa F. Jahn, B.S., Baltimore

In the early years of this century several French workers [1] described a form of hemolytic anemia in which autoagglutination of the patient's red blood cells was frequently observed and a circulating hemolysin often demonstrable. This entity was described as acquired hemolytic anemia to distinguish it from the congenital variety. The concept did not receive widespread acceptance for a number of years, and many such cases were undoubtedly misclassified as hereditary hemolytic anemias. In 1938, Dameshek and associates [2] demonstrated that hemolytic anemias of varying degrees of severity could be experimentally produced by the injection of anti-red-blood-cell serums. The erythrocytes of animals so treated became spherocytic, a characteristic previously considered pathognomonic for the congenital type of hemolytic anemia. Nevertheless, until some seven years ago the demonstration of anti-red-blood-cell antibodies in human beings with hemolytic anemia was possible in only a fraction of the cases. The introduction of new techniques, derived largely from studies on the Rh antigen, altered this situation greatly. A considerable body of immunologic data has accumulated regarding acquired hemolytic anemia. The purpose of this paper is to discuss some recent aspects of the diagnosis and treatment of this disease based on the personal study of 19 such cases and a review of the pertinent literature from 1940 to 1951 inclusive.

From the Department of Medicine, University of Maryland School of Medicine, and the Baltimore Rh Laboratory.

Read before the Section on Internal Medicine at the 101st Annual Session of the American Medical Association, Chicago, June 11, 1952.

1. Widal, F.; Abrami, P., and Brulé, M.: Les ictères d'origine hémolytique, Arch. d. mal. du couer **1**: 193, 1908. Chauffard, A., and Troisier, J.: Anémie grave avec hémolysine dans la sérum, Semaine méd. **28**: 904, 1908.

2. Dameshek, W., and Schwartz, S. O.: Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias, with Particular Reference to the Nature of Spherocytosis and Increased Fragility, Am. J. M. Sc. **196**: 769, 1938.

CLINICAL AND HEMATOLOGICAL ASPECTS

In vitro and in vivo immunologic studies have demonstrated that the basic pathological physiology of acquired hemolytic anemia is an accelerated destruction of the patient's erythrocytes, presumably due to an autoaggl-

tinin firmly attached to the red blood cells and capable, furthermore, of reacting with any normal human erythrocytes. Despite this knowledge, the basic cause remains obscure. The disease may arise in a previously healthy person, or it may be superimposed on an already existing disease. In the former case it is customary to speak of idiopathic acquired hemolytic anemia and, in the latter, of symptomatic hemolytic anemia. With regard to some of the diseases that may be complicated by a hemolytic anemia, an analysis of 85 such cases reported in the literature in the period 1940-1951 revealed that approximately 73% occurred as a complication of primary atypical pneumonia or one of the lymphomas. Of particular interest in the remaining group are those occurring as a complication of one of the "collagen" group of diseases. Dubois [3] has recently suggested that hemolytic anemia may be an important initial manifestation of an underlying disseminated lupus erythematosus. The clinical behavior and management of the symptomatic cases will be dependent to a large extent on the underlying disease process; therefore, this group will be considered separately below.

Idiopathic acquired hemolytic anemia appears to have no particular age predilection, since it has been seen to occur in any age group, though with much less frequency in the eighth and ninth decades of life. This observation was based on a review of 147 cases collected from the literature as well as on the 16 idiopathic cases in our own series. Although the fact has not been noted or stressed heretofore, there is a distinct difference in regard to the sex ratio. Approximately two-thirds of the patients reported on, as well as those of our own series, have been females. The significance of this fact is obscure, but it is of interest to note that in this regard idiopathic acquired hemolytic anemia follows a pattern not unlike the collagen diseases, particularly lupus erythematosus.

The absence of familial hemolytic disease, a negative history with regard to exposure to known hemolytic agents, and the demonstration of the characteristic immunologic findings constitute the basis of the diagnosis of acquired hemolytic anemia. The onset and course vary with the intensity of hemolysis. On the one hand, there may be a sudden onset of profound anemia associated with transient hemoglobinemia and hemoglobinuria. Patients so afflicted appear acutely ill and may be febrile. Pain in the upper abdomen, or more specifically over the left upper quadrant, may be present. Pallor and tachycardia are marked. Jaundice and splenomegaly are usually noted. On the other hand, the onset may be more insidious, with the outstanding clinical findings being slowly progressive weakness, pallor, jaundice, and splenomegaly.

The blood picture usually shows a normocytic anemia, although macrocytosis may be present if reticulocytosis is pronounced. The leukocyte count is either normal or slightly increased. The latter finding is more likely to occur in acute cases and will usually be associated with a "left shift" of the granulocytes. The platelets are usually normal in number. An interesting group of cases has been reported by Evans and co-workers,[4] however, in which both hemolytic anemia and thrombocytopenic purpura have occurred in the same person. One such case was present in our series. Examination of the blood smear reveals spherocytosis, reticulocytosis, and normoblastosis. Accurate red blood cell counting may be difficult because of the spontaneous agglutination of the erythrocytes in the pipet. This phenomenon, noted by an alert observer, may provide the first clue as to the nature of the process.

Biochemical abnormalities consist of elevated indirect plasma bilirubin level and increased urobilinogen excretion in the urine and feces. A certain proportion of patients will have a positive serologic test for syphilis. Because of the pronounced immunologic abnormalities in these cases, this finding should be regarded with suspicion as being perhaps a biologic false positive reaction. In several patients in our series this question was resolved by performance of a Treponema immobilization test.[5] A factor of some diagnostic and therapeutic import is the difficulty often encountered in correctly typing the patient's blood. Because of the marked tendency to autoagglutination, the patient may be incorrectly typed as AB Rh positive. If any suspicion exists, the red blood cells should be thoroughly washed with isotonic sodium chloride solution and typed at 37 C.

IMMUNOLOGIC ASPECTS

The most constant immunologic finding in acquired hemolytic anemia is a positive antihuman globulin (Coombs') test. At first considered characteristic of the acquired form of hemolytic anemia, this test has, on a few occasions, been found positive in certain congenital hemolytic syndromes [6]; nevertheless, when associated with a circulating autoagglutinin, it is strong presumptive evidence in favor of an acquired hemolytic process. The test possesses many technical hazards and should be performed only by a person with considerable experience. An effort has been made to quantitate the adsorbed antibody (quantitative Coombs' test) and correlate it with the clinical status of the patient. Technical precautions with regard to the standardization of the reagent are essential for this procedure.

The serum of these patients usually contains a panagglutinin capable of reacting with any normal human group O red blood cells. In order to demonstrate and characterize it, it is usually necessary to set up agglutination tests at various temperatures and in several media (isotonic sodium chloride solution and bovine albumin solution). If these tests are negative, the red blood cells previously incubated with the patient's serum should be washed and tested with Coombs' serum. This is the indirect Coombs' reaction that may be positive when other methods have failed. Erythrocytes treated with trypsin or papain may also be employed for detection of the abnormal antibody. The study of our series of patients revealed the presence of a positive Coombs' test in all cases. In 16 of the 18 cases tested, panagglutinins or autoagglutinins were found in the serums. Those reacting

3. Dubois, E. L.: Acquired Hemolytic Anemia as the Presenting Syndrome of Lupus Erythematosus Disseminatus, Am. J. Med. **12**: 197, 1952.
4. Evans, R. S., and others: Primary Thrombocytopenic Purpura and Acquired Hemolytic Anemia: Evidence for Common Etiology, A.M.A. Arch. Int. Med. **87**: 48 (Jan.) 1951.
5. Nelson, R. A., Jr., and Mayer, M. M.: Immobilization of Treponema Pallidum in Vitro by Antibody Produced in Syphilitic Infection, J. Exper. Med. **89**: 369, 1949.
6. Wright, C. S., and others: Studies of Hemagglutinins in Hereditary Spherocytosis and in Acquired Hemolytic Anemia: Their Relationship to Hypersplenic Mechanism, J. Lab. & Clin. Med. **37**: 165, 1951.

at 22 and 37 C are termed warm agglutinins, while those reacting at 4 C are cold agglutinins. A considerably lower incidence of free autoagglutinins was noted in the cases collected from the literature. The difference may be due to failure to employ sensitive techniques.

Cold hemagglutinins of low titer occur in virtually all normal human serums and are usually of no pathogenic significance. In cases of acquired hemolytic anemia, the cold agglutinins are present in high titer and are associated with lesser amounts of warm agglutinins and a positive Coombs' test. Although the fact has not been emphasized, it is apparent that hemolytic anemias associated with cold agglutinins have, in the main, a better prognosis than those associated with warm agglutinins. Thus, in a group of 35 cases of hemolytic anemia complicating primary atypical pneumonia, 33 (94%) subsided after symptomatic therapy and subsidence of the pulmonary pathological condition. This is an entirely different picture from that seen in other types of acquired hemolytic anemia. A similar experience was encountered in our series.

We have failed to observe any definite correlation between antibody titer and the severity of the disease process. It is of interest to note that the abnormal antibodies persist in the serum for long periods after splenectomy. This fact was noted in 52 (89.6%) of 58 cases collected from the literature and in 7 (100%) of our patients who had had a splenectomy and were available for follow-up. Antibodies have been found for as long as four and a half to five years after operation. Similar observations have been made with regard to the Coombs' test. In addition to the in vitro observations cited above, an important characteristic of these cases is the rapid destruction of transfused red blood cells in the patient's circulation. Loutit and Mollison,[7] employing the Ashby technique, noted that normal red blood cells became Coombs' positive and disappeared in 10 to 40 days from the recipient's circulation in contrast to a normal life span of approximately 120 days.

MANAGEMENT

As we have previously noted, some patients with acquired hemolytic anemia (notably those with a high titer of cold hemagglutinins) have a relatively benign prognosis and respond to conservative management. Three patients in our series were treated with transfusions and cortisone (100 to 200 mg. daily) alone and went into remission in 7 to 14 days. These patients showed not only clinical and hematological improvement but also striking immunologic improvement. No relapses have occurred to the date of writing. In contrast to these are the patients with warm hemagglutinins. Analysis of 147 cases collected from the literature reveals that remission occurred in only 53 to 55% of the group, whether they had had a splenectomy or not. Immunologic data in many of these cases dating from the first half of the decade are incomplete. Despite the inadequacy of splenectomy, this procedure has, until recently, been the mainstay in the treatment of patients failing to respond to supportive measures. Its use has been based on two hypotheses: (*a*) removal of an organ largely responsible for erythrocyte destruction, and (*b*) the possibility that splenectomy would remove an important source of antibody formation. Evidence previously cited seems to refute the latter hypothesis. The former may be valid, although no quantitative supporting data exist at this time.

During the past two years the treatment of acquired hemolytic anemia has been advanced considerably, owing to the introduction of corticotropin (ACTH) and cortisone. Since this disease is apparently due to an adverse antigen-antibody reaction, the trial of these hormones, known to exert a beneficial effect on diseases of hypersensitive causation, was quite rational. Several groups of investigators[8] have recently reported the successful use of these agents in nine patients with idiopathic or symptomatic hemolytic anemia. Remissions occurred in all cases. Because remission could be maintained only with continued therapy, splenectomy was successfully performed in seven patients. Four subsequently required maintenance therapy with cortisone. Several reports cite a significant reduction in antibody titer coincident with steroid therapy.

Cortisone or corticotropin was employed in eight patients in our series. Two patients went into remission after treatment with transfusions and the steroid hormones. These were both of the cold hemagglutinin variety of acquired hemolytic anemia. Significant improvement was noted in the remaining six. This was characterized by increase in red blood cell count, diminution in reticulocytosis, decrease in jaundice, regression of the enlarged spleen, and decreased antibody titers; however, when it became obvious that remission could only be maintained by continuous cortisone (cortone®) therapy, splenectomy was done. In contrast to the situation in previous years, these patients were in excellent clinical condition at the time of operation. Five of the patients required cortisone for varying periods postoperatively. In three cases it was ultimately possible to discontinue cortisone. Two patients have required continuous therapy for 14 and 18 months respectively. Although the disadvantages of long-continued steroid therapy are not to be ignored, there is no doubt in our minds that, but for the availability of this form of treatment, some of these patients would be dead. Cortisone has been employed successfully in several of our patients with symptomatic hemolytic anemia complicating chronic lymphatic leukemia. One of these patients later had a splenectomy performed with additional benefit.

COMMENT

Despite the increased information that has accumulated recently with regard to the immunologic features of acquired hemolytic anemia, lack of knowledge of the basic causation is a distinct handicap to further progress. The possibility that erythrocytes may become autoantigenic through the action of some agent has been suggested

7. Loutit, J. F., and Mollison, P. L.: Haemolytic Icterus (Acholuric Jaundice), Congenital and Acquired, J. Path. & Bact. **58**: 711, 1946.

8. Dameshek, W.; Rosenthal, M. C., and Schwartz, L. I.: Treatment of Acquired Hemolytic Anemia with Adrenocorticotrophic Hormone (ACTH), New England J. Med. **244**: 117, 1951. Gardner, F. H.; McElfresh, A. E.; Harris, J. W., and Diamond, L. K.: Effect of Adrenocorticotrophic Hormone (ACTH) in Idiopathic Acquired Hemolytic Anemia as Related to Hemolytic Mechanisms, J. Lab. & Clin. Med. **37**: 444, 1951. Davidson, L. S. P.; Duthie, J. J. R.; Girdwood, R. H., and Sinclair, R. J. G.: Clinical Trials of A.C.T.H. in Haemolytic Anemia, Brit. M. J. **1**: 657, 1951.

9. Moolten, S. E., and Clark, E.: The Red Blood Cells as a Vehicle of Virus Transport: II. The Role of Blood-Borne Viruses in Autohemagglutination and in Hemolytic Anemia, Tr. New York Acad. Sc **14**: 232, 1952.

by various workers. Recently, Moolten and Clark [9] have reported the isolation of Newcastle disease virus from the blood of three patients with hemolytic anemia. The possibility that this or some other virus may become firmly attached to the red blood cell and alter its antigenic structure has been suggested. Moolten and Clark also suggest the possibility that the antibody adherent to the red blood cells of these patients and responsible for the positive Coombs' test may be an antiviral antibody rather than an autoantibody. These observations still require confirmation. Studies toward this end are in progress in our laboratory at the time of this writing.

SUMMARY

The clinical, hematological, and immunologic aspects of acquired hemolytic anemia are reviewed. Analyses are based upon 19 patients studied by the authors and 147 cases collected from the literature during the period 1940-1951. The more favorable outlook of patients with acquired hemolytic anemia associated with cold hemagglutinins as compared with those with warm hemagglutinins is stressed. The use of corticotropin (ACTH) and cortisone in combination with other forms of therapy has greatly improved the outlook of patients with this disease.

SYNTHETIC MUSCLE RELAXANTS IN ANESTHESIA

Francis F. Foldes, M.D., Theodore S. Machaj, M.D., Robert D. Hunt, M.D., Pearl G. McNall, M.D., Pittsburgh
and
Phil C. Carberry, M.D., Irvington, N. J.

Analgesia, amnesia or freedom from apprehension, and good muscular relaxation are essential in the anesthetic management of patients for most surgical procedures.[1] Both ether and chloroform, the first two agents used extensively for the production of surgical anesthesia, were able to fulfill these three requirements. Due to this, for almost a century the search for new anesthetic agents was directed toward compounds that would possess all the three properties mentioned but would be free of the unwanted side-effects of ether and chloroform. In the middle 1930's, first cyclopropane [2] and then thiopental (pentothal®) sodium [3] were introduced into anesthesiology, and their use became rapidly popular. It soon became evident, however, that, with regard to muscular relaxation, neither cyclopropane nor thiopental sodium always fulfilled the requirements of good surgical anesthesia.

While the search for new anesthetic agents continued, gradually more information had been gathered on the pharmacologic effects of the general anesthetic agents already in use and on the pathological changes that occasionally followed their administration. Chloroform was the first to fall victim to the findings of these investigations.[4] In recent years, however, more and more evidence became available that ether, the old stand-by of anesthesiologists, was not a harmless agent under all circumstances. The changes of intermediary metabolism (such as hyperglycemia and glycopenia [5]) that accompany ether anesthesia have long been known. It has also been demonstrated that deep ether anesthesia, necessary for the production of muscular relaxation, can interfere with kidney [6] and liver [7] function and decreases myocardial efficiency in laboratory animals.[8] Ether can adversely effect cardiac function in man in the presence of myocardial damage.[9] The effect of deep ether anesthesia on the homeostatic mechanism responsible for the maintenance of blood pressure has also been demonstrated.[10] The opinion of many anesthesiologists was recently expressed by Gillies,[11] who stated, "In many clinics, uncompensated depression of respiratory and circulatory functions, seen at its worse in third or fourth plane ether anesthesia and regarded as ideal for abdominal surgery, became routine. . . . In submitting to operations involving vital functions directly or indirectly to an extent never before known, patients had enough to overcome on their way to recovery without the extra burden of the metabolic, respiratory and cardiovascular disturbances added by prolonged general anesthesia."

As early as 1914, Crile [12] advocated the simultaneous use of more than one anesthetic agent. Bennett,[13] in 1939, introduced the use of purified chondodendron tomentosum extract (intocostrin®), the first standardized curare preparation, to clinical medicine. Shortly thereafter, Lundy [14] reemphasized the concept of balanced anesthesia, and the stage was set for the addition of muscle relaxants to the armamentarium of the anesthesiologist. Considering the relatively poor muscle relaxing property of cyclopropane, it is not surprising that it was left to Griffith,[15] one of the foremost exponents of cyclopropane anesthesia, to introduce curare into anesthesiology and thereby open a new chapter in the development of this field of medicine.

The purpose of the use of curare and its derivatives has been to obtain muscular relaxation in relatively light planes of general anesthesia with agents that produce a selective blockade of neuromuscular transmission. It soon became evident, however, that curare does not possess such a selective action, and its administration also affects preganglionic autonomic transmission [16] and is responsible for the liberation of histamine.[17] These unwanted side-effects of the curare derivatives that occasionally produced severe fall in blood pressure [18] and bronchiolar spasm [19] stimulated the search for other compounds with greater selective action on neuromuscular function.

Because of space limitations, the bibliographic references have been omitted from THE JOURNAL and will appear in the authors' reprints.

Read in the Symposium on Relaxants before the Section on Anesthesiology at the 101st Annual Session of the American Medical Association, Chicago, June 11, 1952.

From the Department of Anesthesiology of the Mercy Hospital and the Section of Anesthesiology, Department of Surgery, University of Pittsburgh School of Medicine.

PHARMACOLOGY

Due to the pioneering work of Bovet [20] and his associates, of Ing and Barlow,[21] of Paton and Zaimis,[22] of Cavallito and co-workers,[23] of Hoppe,[24] and of others since 1946, numerous compounds were synthesized that were capable of blocking neuromuscular transmission. All these compounds are characterized by the presence of more than one quaternary ammonium group placed about 15 Å. apart in the molecule.[25] Depending on their mode of action, they can be divided into two groups.[26] The members of the first group act similarly to tubocurarine (*d*-tubocurarine) chloride and block neuromuscular transmission by inhibiting the physiological depolarization of the postjunctional membrane caused by acetylcholine. The members of the second group produce persistent depolarization and thereby prevent the physiological depolarization-repolarization sequence caused by the acetylcholine-acetylcholine esterase system that is necessary for unimpaired neuromuscular transmission (fig. 1). It is not improbable that compounds of a third group possess both an antidepolarizing effect and a persistent depolarizing effect of their own.[27]

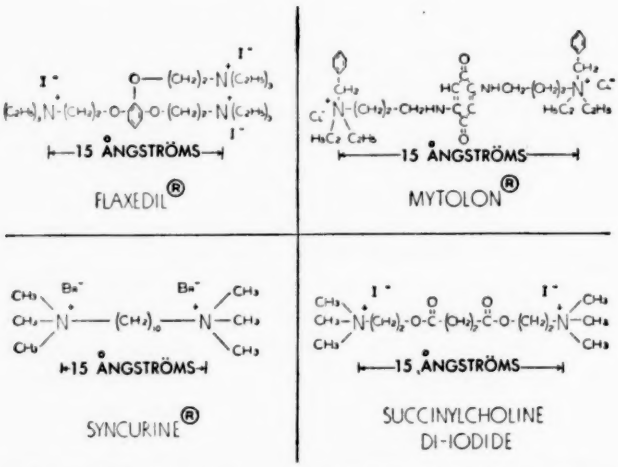

Fig. 1.—Structural formulas of synthetic muscle relaxants. Neuromuscular blockade is associated with presence of quaternary nitrogen atoms 15 Å. apart.

Of the great number of synthetic muscle relaxants made available by the chemists and studied by the pharmacologists, decamethonium (syncurine®) bromide, benzoquinonium (mytolon®) chloride, gallamine (flaxedil®) triethiodide, and, most recently, succinylcholine, have been used in clinical anesthesiology. Gallamine triethiodide belongs to the group of antidepolarizing agents; decamethonium bromide and succinylcholine cause persistent depolarization; and benzoquinonium chloride probably is one of the intermediary compounds mentioned (fig. 2). All four compounds are freely soluble in water, are readily miscible with other drugs commonly used in anesthesiology, and can be sterilized by autoclaving. They can be stored at room temperature without loss of potency for prolonged periods.

The pharmacologic properties of decamethonium bromide,[28] benzoquinonium,[29] gallamine,[30] and succinylcholine [31] have been studied extensively. It has been shown that there is a considerable species variation in the potency of these compounds (fig. 3). From the clinicians' point of view, it is of interest that the susceptibility of the various muscle groups toward different agents need not be the same. According to Paton,[32] the sensitivity of the pharyngeal, laryngeal, and facial muscles to decamethonium bromide is less than to tubocurarine, and the situation is reversed as far as the muscles of the trunk are concerned. Another fact that became evident from these pharmacologic studies was that the depolarizing type agents (succinylcholine and decamethonium bromide) show a greater specificity towards neuromuscular transmission and, in therapeutic doses, have no effect on autonomic synaptic transmission. In contrast to this, gallamine possesses an atropine-like effect on the

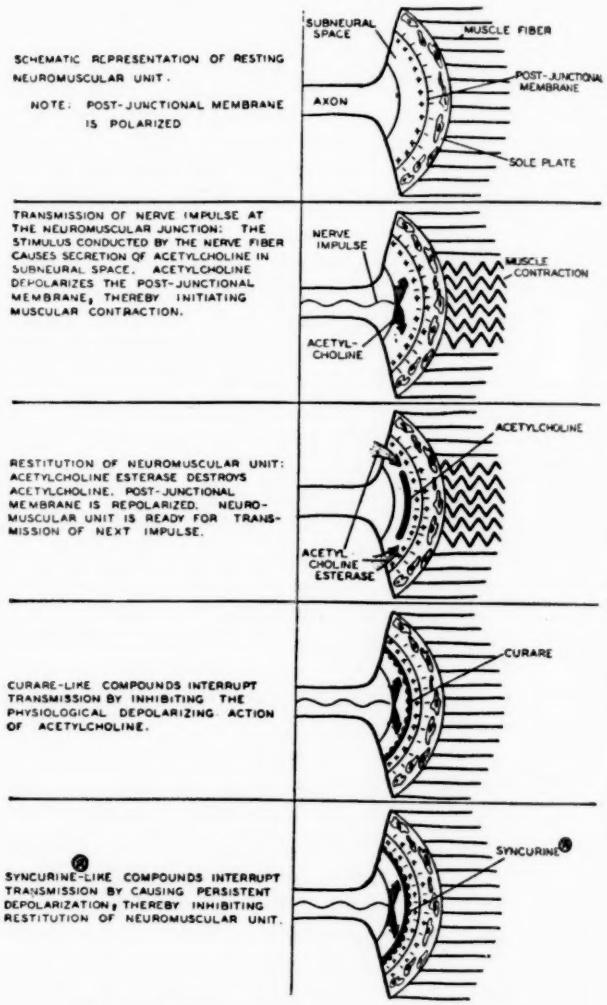
SCHEMATIC REPRESENTATION OF RESTING NEUROMUSCULAR UNIT.
NOTE: POST-JUNCTIONAL MEMBRANE IS POLARIZED
SUBNEURAL SPACE
MUSCLE FIBER
AXON
POST-JUNCTIONAL MEMBRANE
SOLE PLATE
TRANSMISSION OF NERVE IMPULSE AT THE NEUROMUSCULAR JUNCTION: THE STIMULUS CONDUCTED BY THE NERVE FIBER CAUSES SECRETION OF ACETYLCHOLINE IN SUBNEURAL SPACE. ACETYLCHOLINE DEPOLARIZES THE POST-JUNCTIONAL MEMBRANE, THEREBY INITIATING MUSCULAR CONTRACTION.
NERVE IMPULSE
MUSCLE CONTRACTION
ACETYL-CHOLINE
RESTITUTION OF NEUROMUSCULAR UNIT: ACETYLCHOLINE ESTERASE DESTROYS ACETYLCHOLINE. POST-JUNCTIONAL MEMBRANE IS REPOLARIZED. NEUROMUSCULAR UNIT IS READY FOR TRANSMISSION OF NEXT IMPULSE.
ACETYLCHOLINE
ACETYL-CHOLINE ESTERASE
CURARE-LIKE COMPOUNDS INTERRUPT TRANSMISSION BY INHIBITING THE PHYSIOLOGICAL DEPOLARIZING ACTION OF ACETYLCHOLINE.
CURARE
SYNCURINE-LIKE COMPOUNDS INTERRUPT TRANSMISSION BY CAUSING PERSISTENT DEPOLARIZATION, THEREBY INHIBITING RESTITUTION OF NEUROMUSCULAR UNIT.
SYNCURINE®

Fig. 2.—Pharmacology of neuromuscular conduction.

cardiac vagus,[30] and benzoquinonium has muscarinic effect on the vagus. No evidence of histamine release was observed with any of the synthetic muscle relaxants in clinical use. Another point of importance with regard to the clinical application of these agents is their fate in the organism. Gallamine, benzoquinonium, and decamethonium bromide, similarly to tubocurarine, are excreted largely unchanged by the kidneys.[33] In contrast to this, succinylcholine is hydrolyzed by both the plasma cholinesterase and the true acetylcholine esterase [34] to pharmacologically inert choline and succinic acid.

MATERIAL AND METHODS

The use of decamethonium bromide,[35] benzoquinonium chloride,[36] gallamine triethiodide,[37] and succinylcholine [38] was observed in 204, 155, 339, and 153 patients, respectively. No selection was made with regard to the physical condition of the patient, except that patients with known allergies (e. g., bronchial asthma) in whom the administration of thiopental sodium was contraindicated were excluded from this study. The muscle relaxant under investigation at the time was used in consecutive groups of cases. To be able to form an opinion of the muscle relaxing properties of these compounds, only patients undergoing intra-abdominal operations were included in this study. For similar reasons, general anesthesia was maintained by combinations of thiopental sodium and nitrous oxide-oxygen alone. The age distribution (table 1) and the frequency of the various surgical procedures (table 2) were similar with all agents. The operations were performed by the same group of surgeons in one hospital, and all anesthesias were carried out by similar techniques, supervised by one person (F. F. F.).

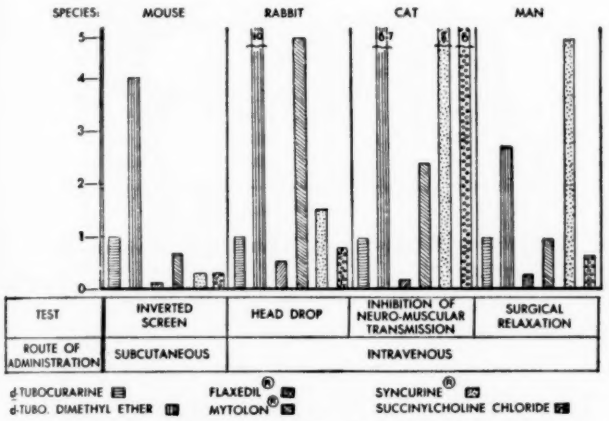

Fig. 3.—Relative potency of muscle relaxants in various species.

PREMEDICATION

From 50 to 200 mg. of pentobarbital was given by mouth or by intramuscular injection of its sodium salt 60 to 90 minutes before the start of anesthesia. Thirty minutes later, 0.2 to 0.6 mg. of scopolamine hydrobromide or atropine sulfate was administered subcutaneously, together with 5 to 15 mg. of morphine sulfate or 50 to 100 mg. of meperidine (demerol®) hydrochloride. As suggested by Arrowood,[39] relatively larger doses of scopolamine or atropine were administered when the muscle relaxant in use was benzoquinonium chloride.

ANESTHETIC MANAGEMENT

On arrival at the operating room, the patient's mouth, nasopharynx, and oropharynx were sprayed with 1% tetracaine (pontocaine®) hydrochloride solution. An intravenous infusion with 5% dextrose injection in isotonic sodium chloride solution or in water was started. All subsequent injections were made through the rubber sleeve of the intravenous tubing. When the muscle relaxant was decamethonium bromide or succinylcholine, stage 3, plane 1 or 2 anesthesia was induced by the intravenous administration of a 2.5% thiopental sodium solution. This was followed by the estimated dose of decamethonium bromide (1 to 4 mg.) or succinylcholine diiodide (15 to 45 mg.). When the muscle relaxant used was benzoquinonium chloride or gallamine triethiodide, the estimated dose (4.5 to 18 mg. and 40 to 80 mg., respectively) was given first and the administration of thiopental sodium was started only when the patients showed signs of incipient muscular paralysis. After satisfactory muscular relaxation developed, the cords were visualized by direct laryngoscopy and sprayed with a 1% tetracaine solution. If at this time the cords were wide open and did not react to the stimulus of spraying, an endotracheal tube was inserted. If the laryngeal reflex was still active, an oral airway was inserted and oxygen administered by mask for one to two minutes to allow the tetracaine to exert its topical anesthetic effect; then the cords were again visualized and the patients intubated. Additional doses of thiopental sodium were administered during this time, when necessary. Following intubation, a face mask was applied; and, after a few breaths of oxygen, the bag of the anesthesia machine was allowed to fill up three times in succession with a mixture of 3 liters of nitrous oxide and 1 liter of oxygen (a 3:1 ratio).[40] When the bag was filling up the fourth time, the administration of a mixture of 500 cc. of nitrous oxide and 500 cc. of oxygen per minute was started. Such a mixture delivered to the patient approximately 30% oxygen and 70% nitrous oxide. From then on, additional thiopental sodium was given intermittently as required. In the patients receiving benzoquinonium, gallamine, or succinylcholine, 25 to 100 mg. of meperidine hydrochloride in divided doses was given intravenously to decrease the patient's thiopental sodium requirements. Fractional doses of decamethonium bromide (0.5 to 1 mg.), benzoquinonium (1.5 to 6 mg.), or gallamine (10 to 30 mg.) were administered at 10 to 30 minute intervals. The last dose

TABLE 1.—*Age Distribution of Patients Receiving Muscle Relaxants in Anesthesia*

Age Group, Yr.	Syncurine®		Mytolon® Chloride		Flaxedil®		Succinylcholine Di-Iodide	
	No.	%	No.	%	No.	%	No.	%
11-20	10	4.9	2	1.3	11	3.2	4	2.6
21-30	24	11.8	18	11.6	31	8.9	13	8.4
31-40	32	15.7	20	12.9	68	20.1	26	16.7
41-50	47	23.0	39	25.1	84	24.9	42	28.4
51-60	44	21.6	35	22.6	81	24.0	35	22.4
61-70	36	17.6	30	19.4	46	13.6	21	13.7
71-80	10	4.9	11	7.1	17	5.0	9	5.8
81-90	1	0.5	0	0	1	0.3	3	2.0
Total	204	100.0	155	100.0	339	100.0	153	100.0

TABLE 2.—*Types of Operation in Which Muscle Relaxants Were Used*

Operations	Syncurine®		Mytolon® Chloride		Flaxedil®		Succinylcholine Di-Iodide	
	No.	%	No.	%	No.	%	No.	%
Gastric surgery.....	17	8.3	28	18.0	71	21.0	31	20.2
Gallbladder surgery..	84	41.2	64	41.2	121	35.6	45	29.5
Other upper abdominal surgery.....	26	12.7	31	20.0	49	14.5	30	19.6
Large bowel surgery	15	7.4	9	5.8	19	5.6	16	10.4
Appendectomy.....	36	17.6	10	6.5	41	12.1	7	4.6
Intra-abdominal gynecologic operations..	26	12.8	13	8.5	38	11.2	24	15.7
Total.....	204	....	155	....	339	....	153	....

of muscle relaxant was usually given five minutes before the start of peritoneal closure. Succinylcholine was administered in the form of a continuous intravenous drip (20 to 120 drops per minute) of a 0.2% solution of its di-iodide salt through a no. 23 needle inserted into the rubber sleeve of the intravenous tubing. The infusion was stopped after fascial closure. The tracheobronchial tree was cleared by suction before extubation. Assisted respiration was used throughout, with the exception of those cases in which transient respiratory arrest necessitated controlled respiration. If, at the end of anesthesia, respiratory exchange was inadequate, the patient was kept in the operating room, and assisted respiration was continued until the respiratory tidal volume became normal. No antagonist (such as neostigmine [prostigmin®] or edrophonium ["tensilon"] chloride) was used in any of the cases reported here.

lamine, decamethonium bromide, and benzoquinonium. The effect of a single dose was the shortest with succinylcholine (three to five minutes) and progressively longer with decamethonium bromide, benzoquinonium, and gallamine. In accordance with this, for the maintenance of adequate clinical relaxation, succinylcholine had to be administered by continuous intravenous drip, and the average time interval between the administration of fractional doses was the shortest with decamethonium bromide, longer with benzoquinonium, and the longest with gallamine. The differences in the duration of action of the four agents was also indicated by the dose of relaxant administered per minute of anesthesia time, which was found to be 0.09 mg. for decamethonium bromide, 0.28 mg. for benzoquinonium, 3.9 mg. for succinylcholine di-iodide, and 1.38 mg. for gallamine. These doses are in a ratio of 15:5:0.4:1 on a milligram basis and in a

TABLE 3.—*Muscle Relaxant and Thiopental Sodium Requirements*

	Syncurine®		Mytolon® Chloride		Flaxedil®		Succinylcholine Di-Iodide	
	Range	Average	Range	Average	Range	Average	Range	Average
Duration of anesthesia, min.	25-480	95	15-330	126	40-335	122	35-327	125
Initial dose of relaxant, mg.	1.0-4.0	2.4	4.5-18.0	12.3	40.0-100.0	74.0	10-50	28.8
Development of maximal effect, min.	4-6	...	6-8	...	3-5	...	1-2	...
Fractional dose of relaxant, mg.	0.5-1.0	...	1.5-6.0	...	10.0-30.0	...	Administered in continuous intravenous drip	
Time between fractional doses, min.	10-20	...	15-20	...	15-30	...		
Muscle relaxant used per minute, mg.	0.02-0.36	0.09	0.09-1.40	0.28	0.40-2.86	1.38	1.11-9.20	3.90
Initial dose of thiopental sodium, mg.	200-850	493	175-1,000	510	200-900	484	300-1,000	553
Dose of thiopental sodium per minute, mg.	2.7-28.8	13.4	2.4-25.0	10.3	3.1-25.8	10.5	13.3	2.4-34.8

TABLE 4.—*Apnea During Anesthesia, Postanesthetic Recovery Time, and State of Respiration at Termination of Anesthesia with Use of Various Muscle Relaxants*

	Syncurine®		Mytolon® Chloride		Flaxedil®		Succinylcholine Di-Iodide	
	Range	Average	Range	Average	Range	Average	Range	Average
Incidence of apnea, %	.....	21.0	.....	12.4	.....	13.6	.....	0
Duration of apnea, min.	3-22	9.5	9-60	10	2-25	6.3	0	0
Patients reacting at end of anesthesia, %	.....	17.1	.....	67.0	.....	70.0	.....	58.0
Recovery time in remainder of patients, min.	5-184	35	5-120	33	5-210	48	5-345	81
State of respiration at termination of anesthesia	Satisfactory 76% Depressed 24%		Satisfactory 88% Depressed 12%		Satisfactory 75% Depressed 25%		Satisfactory 100% Depressed 0%	

RESULTS

The intravenous injection of decamethonium bromide rarely, or that of succinylcholine frequently, was followed by fasciculatory muscle movements. These fasciculatory movements caused by the depolarizing action of these compounds could be avoided by a slow rate of injection. The dose and time relationships of the various muscle relaxants are summarized in table 3. The average initial dose that produced adequate muscular relaxation for intubation and the opening of the peritoneum was 2.4 mg. for decamethonium bromide, 12.3 mg. for benzoquinonium chloride, 74 mg. for gallamine triethiodide, and 28.8 mg. for succinylcholine di-iodide. In other words, as far as initial relaxation is concerned on a milligram basis, the relative potencies of decamethonium bromide, benzoquinonium, succinylcholine di-iodide, and gallamine compared to one another as 31:6:2.5:1. On a molar basis, their relative potency was 15:4:1.5:1. After administration of the initial dose, maximal effect developed in the following order: first, succinylcholine, then gal-

ratio of 7.5:3.5:0.2:1 on a molar basis. The average dose of thiopental sodium before intubation was 493 mg. with decamethonium bromide, 510 mg. with benzoquinonium, 484 mg. with gallamine, and 556 mg. with succinylcholine di-iodide.

With the above dosage, adequate muscular relaxation could be obtained in all patients; however, not without the development of apnea in some cases (table 4). The incidence of this unwanted side-effect was 21%, 12.4%, and 13.6%, with an average duration of 9.5, 10, and 6.3 minutes for decamethonium bromide, benzoquinonium, and gallamine, respectively. For reasons to be discussed later, no respiratory arrest lasting longer than 20 to 30 seconds was observed with succinylcholine, unless produced deliberately for teaching purposes. With adequate muscular relaxation, a certain degree of respiratory depression, requiring assisted respiration, was almost always present with decamethonium bromide, benzoquinonium, and gallamine but was frequently absent with succinylcholine.

The percentage of patients reacting to stimulation after extubation, the recovery time of the remainder of the patients, and the state of respiration at the end of anesthesia are summarized in table 4. As far as postanesthetic recovery was concerned, gallamine and benzoquinonium were superior to decamethonium bromide and succinylcholine. With regard to postoperative respiratory depression, however, succinylcholine was far superior to the other three agents. Prolonged postanesthetic respiratory depression lasting from 30 to 180 minutes was found on four, three, and four occasions after the use of decamethonium bromide, benzoquinonium, and gallamine, respectively. The circulatory changes observed with the administration of the various muscle relaxants are presented in tables 5 and 6.

The effect of the muscle relaxants on pulse rate and blood pressure can be observed most clearly if the preanesthetic values are compared with those obtained 10 minutes after the start of and at the end of anesthesia, since these values are not influenced by the autonomic reflexes caused by surgical manipulation. The average pulse rate was practically unchanged 10 minutes after the administration of decamethonium bromide and benzoquinonium; it was slightly elevated after succinylcholine and somewhat more increased after gallamine. Similarly, there was little or no change in pulse rate at the end of anesthesia with decamethonium bromide or benzoquinonium, a slight elevation with succinylcholine, and a more pronounced rise with gallamine. There was no significant change in the systolic and diastolic blood pressure values after 10 minutes or at the end of anesthesia, except for a moderate elevation of both with decamethonium bromide and gallamine. Bronchospasm or other evidence of histamine release was not observed with any of the four muscle relaxants used. Excessive salivation and bronchial secretion were occasionally seen with benzoquinonium when the dose of the preoperative parasympatholytic agent was inadequate or had worn off. Hiccuping, which was occasionally seen with the use of decamethonium bromide, benzoquinonium, and succinylcholine when traction was exerted on the stomach or duodenum, was seldom encountered with gallamine. The incidence of postoperative atelectasis was 5.4% with decamethonium bromide, 4.5% with benzoquinonium, 1.5% with gallamine, and 2% with succinylcholine, but it is doubtful if any significance can be attached to the above differences. The incidence of excessive bronchial secretions was definitely greater with benzoquinonium than after the use of the other three agents.

There was one anesthetic death in this series in an 81-year-old woman who had diffuse abdominal carcinomatosis with intestinal obstruction. She was admitted a few hours prior to operation in congestive failure, markedly dehydrated, and disoriented. Attempts were made to digitalize the patient with strophanthin preoperatively. Forty milligrams of gallamine were given intravenously, followed by 6 cc. of a 2.5% thiopental sodium solution. During a smooth intubation, cardiac arrest developed that resisted resuscitative measures. There were 19 postoperative deaths in this series of 851 patients. Most of those patients who died had a hopeless prognosis, and no connection could be established between the fatal outcome and the effect of the muscle relaxant in any case.

TABLE 5.—*Changes in Pulse Rate with Use of Various Muscle Relaxants*

Pulse Rate	Syncurine®		Mytolon® Chloride		Flaxedil®		Succinylcholine Di-Iodide	
	Range	Average	Range	Average	Range	Average	Range	Average
Initial	60-135	87	60-150	87	52-130	89	58-136	87
10 min. after start of anesthesia	60-135	89	60-158	88	72-155	97	48-180	92
Lowest value observed during anesthesia	50-140	82	40-140	75	53-118	88	48-120	83
Highest value observed during anesthesia	65-140	98	60-158	97	75-155	111	70-180	106
At the termination of anesthesia	60-140	88	50-140	85	70-172	99	60-140	93

TABLE 6.—*Changes in Blood Pressure with Use of Various Muscle Relaxants*

Systolic Blood Pressure	Syncurine®		Mytolon® Chloride		Flaxedil®		Succinylcholine Di-Iodide	
	Range	Average	Range	Average	Range	Average	Range	Average
Initial	75-185	114	70-230	121	72-240	120	80-300	123
10 min. after start of anesthesia	60-220	119	60-220	116	60-230	118	74-228	119
Lowest value observed during anesthesia	40-150	105	50-180	100	65-160	108	68-222	107
Highest value observed during anesthesia	80-220	130	80-256	135	95-230	139	84-280	139
At termination of anesthesia	68-210	126	60-210	122	80-210	128	85-200	124
Diastolic Blood Pressure								
Initial	40-110	68	32-120	73	40-120	72	40-142	76
10 min. after start of anesthesia	40-130	74	40-130	69	40-140	74	38-118	75
Lowest value observed during anesthesia	20-110	65	20-102	81	20-100	66	38-118	66
Highest value observed during anesthesia	40-130	82	50-130	59	50-150	91	62-160	89
At termination of anesthesia	40-120	74	40-110	74	40-120	80	40-122	74

COMMENT

The most important single factor determining the indications and contraindications of the various muscle relaxants is their controllability, which in turn depends on their fate in the organism. With the exception of succinylcholine, all the muscle relaxants are excreted mostly unchanged through the kidneys.[33] In contrast to this, succinylcholine is hydrolyzed fairly rapidly by both the plasma cholinesterase and acetylcholine esterase.[34] It is of interest that the rate of hydrolysis of succinylcholine

was found to be much higher in human plasma than in cat or dog plasma.[41] In agreement with this, the milligram dose of succinylcholine per kilogram of body weight was found to be about 10 times larger in man than in cat or dog.[42] It is conceivable that the considerable species variation of other muscle relaxants (fig. 3) might also be explained on the basis of a species variation in cholinesterase activity on one hand and the anticholinesterase activity of these compounds on the other.

The initial dose of muscle relaxants in anesthesiology is determined on an empirical basis. In view of the considerable variation in the sensitivity of different persons to muscle relaxants, errors in judgment are unavoidable. Since the development of the maximal effect of the muscle relaxants (other than succinylcholine) takes two to eight minutes, the respiratory arrest caused by an overdose, or the inadequate relaxation due to an insufficient first dose, will not be manifest immediately. Similarly, considerable variation exists in different persons with the same muscle relaxant, with regard to the duration of the effect of the first dose and the size of the fractional dose necessary to maintain adequate muscular relaxation. Consequently, even the experienced anesthesiologist cannot always be certain that he has been administering the muscle relaxant correctly before he observes the effects of the initial and the first fractional dose. Even then, in a small percentage of cases, prolonged and profound respiratory depression can be encountered at the termination of anesthesia.[43]

Because of the rapid onset of the action of succinylcholine, any error in dose becomes manifest within one to two minutes; and, because of its rapid enzymatic hydrolysis, any error, if not extreme,[44] corrects itself within one to five minutes. Instead of fractional doses, the maintenance dose is administered in the form of a continuous intravenous drip at a speed that maintains optimal relaxation without undue respiratory depression. The degree of relaxation can be adapted to the surgeons' need within one-half to one minute by changing the rate of infusion. Both its relaxant effect and its influence on the respiratory depth completely disappear within five minutes after its administration is discontinued. So far, no postanesthetic respiratory depression has been encountered with succinylcholine.

Besides its exceptional controllability, succinylcholine is also characterized by the paucity of side-effects that accompany its use. Except for a mild vagolytic effect manifested by a slight increase in pulse rate (table 5) and pupillary dilatation seen occasionally, no side-effects accompanied its use. For practical purposes its effects were limited to the inhibition of neuromuscular conduction. In contrast to this, besides the already mentioned prolonged postanesthetic respiratory depression seen occasionally with the other three agents, marked inhibition of the cardiac vagus could be encountered with gallamine triethiodide, and bothersome increase of bronchial secretions was frequently observed with benzoquinonium chloride. The latter two side-effects can outlast considerably the neuromuscular effect of these agents.

Another important difference between succinylcholine and the other synthetic muscle relaxants has been in the quality of respiration. The respiratory movements in general were smoother with succinylcholine; and, because of its more sensitive controllability, good relaxation together with adequate respiratory exchange could be frequently obtained without the use of assisted respiration. The character of respiration with gallamine resembled that seen with succinylcholine the most closely. In our experience, however, with the exception of succinylcholine, assisted respiration was necessary with all the synthetic muscle relaxants, and also with tubocurarine to insure adequate respiratory exchange in the presence of good muscular relaxation. The explanation of the difference in the respiratory effects of succinylcholine from the other relaxants might be found in the observations of Ellis and associates,[45] who reported that the depressant effect exerted by decamethonium bromide and tubocurarine chloride on the respiratory center was more pronounced and of much longer duration than that seen after succinylcholine.

The use of various antagonists has been advocated to overcome the prolonged respiratory depressant effect of muscle relaxants [46] and to terminate muscular relaxation and respiratory depression after endoscopy [47] and electroshock therapy.[48] No serious objections can be raised against the use of anticurare agents if, following their administration, the patients are kept under observation. However, unwanted side-effects (e. g., salivation, bradycardia, hypotension, and bronchospasm) have been occasionally observed with edrophonium chloride[49]; and the same complications, together with increased intestinal motility, have been seen more frequently with neostigmine. On the other hand, the dangers inherent to the use of anticurare agents, when administered to patients subsequently left under insufficient supervision, far outweigh their advantages. Because of the relatively short lasting effect of these agents,[49] it can happen that adequate respiration is only restored temporarily and respiratory depression recurs. Fatalities have been reported after the use of neostigmine.[50] It is our opinion that preference should be given to muscle relaxants, like succinylcholine, which, when administered correctly, do not produce prolonged postanesthetic respiratory depression. Should respiratory depression be encountered after the use of other muscle relaxants, we believe it is safer to administer 100% oxygen with assisted respiration until the return of adequate spontaneous respiratory exchange.

In the series of cases presented, prolonged postoperative respiratory depression occurred in the debilitated and dehydrated patients with clinical signs of potassium deficiency. In a few cases in which prolonged postoperative respiratory depression developed following the use of benzoquinonium or gallamine, it has been our impression that recovery of adequate respiration was hastened by the intravenous administration of a 0.3% potassium chloride solution at the rate of 100 to 120 drops per minute.[51] This observation is in agreement with the findings of Wilson and Wright [52] that potassium antagonizes the neuromuscular block caused by curare. It might be mentioned that, according to Paton and Zaimis,[28] potassium has no antagnostic effect on neuromuscular blockade produced by decamethonium bromide.

With the exception of the already mentioned elevation of pulse rate and blood pressure with the use of gallamine,

the incidence of circulatory changes with the use of these muscle relaxants was low. This is indicated by the figures of tables 5 and 6, which show that there was practically no variation in the pulse rate and blood pressure observed before the start of and at the end of anesthesia. The circulatory changes seen with gallamine although significant, did not have any immediate or delayed ill effect in any of our patients. Despite this, in agreement with Artusio and co-workers,[49] the use of gallamine is not recommended in the presence of cardiovascular disease.

The quantities of thiopental sodium used per minute of anesthesia time was somewhat greater with decamethonium bromide and succinylcholine than with benzoquinonium or gallamine. The reason for this in the case of decamethonium bromide might be that in this series the anesthesia was not supplemented by the use of intravenously administered meperidine hydrochloride as it has been done with the other three agents. At the present time we have no adequate explanation for the greater amount of thiopental sodium necessary for the maintenance of comparable depth of anesthesia with succinylcholine. The possibility cannot be excluded that, bound to choline, the succinate molecule passes the blood-brain barrier after intravenous administration and exerts an antagonistic effect on barbiturate anesthesia. Such effects of succinates have been suggested by Soskin and Taubenhaus,[53] although most other investigators failed to demonstrate this phenomenon either in man or in laboratory animals.[54] Recently, however, Price [55] showed by the use of electroencephalography in dogs that the intracarotid injection of relatively small doses of succinates increased the electrical activity of the cortex under barbiturate anesthesia.

The average dose of thiopental sodium used before endotracheal intubation was greater with benzoquinonium and succinylcholine than with the other two agents. It has been our impression that with succinylcholine more barbiturate was necessary to obtain comparable depth of anesthesia and that with benzoquinonium, probably because of its vagus stimulating effect, a deeper plane of anesthesia was necessary for smooth endotracheal intubation. Because of the larger quantities of thiopental sodium used per minute of anesthesia time, a significantly smaller percentage of patients reacted after extubation with decamethonium bromide than after extubation with the other three agents. Although the number of patients reacting to stimulation at the termination of anesthesia was only slightly less with succinylcholine than with benzoquinonium or gallamine, the sleeping time was considerably increased in the remainder of the patients in whom succinylcholine was used.

The jaw musculature was found to be better relaxed with the use of benzoquinonium and gallamine than with decamethonium bromide or succinylcholine. Since neither thiopental sodium and nitrous oxide nor any of the synthetic muscle relaxants abolish reflex irritability of the vagus, topical anesthetization of the pharynx, larynx, and trachea was found to be important before endotracheal intubation. In the cases in which topical anesthesia was omitted or was inadequate, endotracheal intubation was frequently followed by reflex breath holding that was difficult to distinguish from apnea produced by muscle relaxants. This could be demonstrated repeatedly by the fact that the administration of additional thiopental sodium was often followed immediately by the return of spontaneous respiration.

The reason for also expressing the relative potency of the muscle relaxants used on a molar basis has been that the displacement of acetylcholine from the chemoreceptors of the postjunctional membrane, which is the basic mechanism responsible for the inhibition of neuromuscular transmission with all muscle relaxants, is a molecular reaction. Therefore, by expressing the potency on a molar instead of a milligram basis, a truer picture can be obtained of the relative affinity of these compounds to the cholinergic receptors. It is evident from table 7 that, with the exception of the milligram per minute dose of succinylcholine di-iodide, the potency variation is considerably less on a molar than on a milligram basis.

By reporting on the use of synthetic muscle relaxants only in conjunction with thiopental sodium–nitrous oxide–oxygen anesthesia, it is not implied that their use is not

TABLE 7.—*Potency Variation of Synthetic Muscle Relaxants*

		Syncurine®	Mytolon® Chloride	Succinylcholine Di-Iodide	Flaxedil® *
Based on initial dose, expressed in	Mg.	31.0	6.0	2.5	1.0
	Mol.	15.0	4.2	1.5	1.0
Based on mg./min. dose, expressed in	Mg.	15.0	5.0	0.4	1.0
	Mol.	7.5	3.5	0.2	1.0

* The potency of flaxedil® was chosen as unity.

TABLE 8.—*Conversion Factors for Calculation of Initial and Fractional Doses of Muscle Relaxants with Ether or Cyclopropane from Doses Recommended with Thiopental Sodium–Nitrous Oxide–Oxygen Anesthesia*

Agent	Flaxedil®	Mytolon® Chloride	Syncurine®	Succinylcholine Di-Iodide
Ether	0.6	0.6	1.0	1.0
Cyclopropane	0.8	0.8	1.0	1.0

indicated with other general anesthetic agents. They serve a useful purpose in conjunction with cyclopropane and other anesthesias as attested by the numerous publications that cannot be quoted here. It has been our experience that the doses of decamethonium bromide and succinylcholine are the same with ether or cyclopropane as with thiopental sodium–nitrous oxide–oxygen anesthesia; the doses of benzoquinonium and gallamine have to be reduced more with ether and less with cyclopropane. Table 8 gives the conversion factors from the doses recommended with thiopental sodium–nitrous oxide–oxygen anesthesia to ether and cyclopropane.

The advantages of succinylcholine have been its easy controllability; the absence of apnea during, and of prolonged respiratory depression following, its administration; and the paucity of side-effects that accompany its use. Its only apparent disadvantage has been that, because of the somewhat greater quantities of thiopental sodium used in conjunction with it, the postoperative sleeping time was prolonged in some patients. It should be the first choice when the use of a muscle relaxant is indicated, especially so in old and poor risk patients. It

is the ideal agent for the production of muscular relaxation before endotracheal intubation in cases in which relaxation either is not required for the operative procedure or is to be maintained by ether. At present there are no known contraindications to its use. Besides anesthesiology, it should be the muscle relaxant of choice in conjunction with electroshock therapy and in the treatment of spastic conditions.

Decamethonium bromide is still a useful agent to be administered in a single dose for the production of muscular relaxation of relatively short duration: for example, for endoscopy or before peritoneal closure in cases in which the effect of spinal anesthesia has worn off or in which it is not desirable to deepen the plane of general anesthesia. It is not the best agent for the maintenance of muscular relaxation for lengthy operations, because occasionally its effect between fractional doses tends to wear off abruptly.[35]

Benzoquinonium chloride, carefully administered, gives good relaxation for prolonged surgical procedures. Because of its very low cardiotoxic effect,[29] it is the first choice of the long-acting muscle relaxants in patients with cardiovascular conditions, with the exception of atrioventricular or interventricular block, in which its vagotonic effect would be undesirable. Because of its stimulating effect on postoperative bronchial secretions, it is contraindicated in respiratory diseases.

Of all the long-acting muscle relaxants, gallamine triethiodide has been our choice for use in long operations requiring good muscular relaxation. With comparable relaxation it has a greater sparing effect on respiration than decamethonium bromide. Because of the consistent tachycardia, which is not as pronounced when used with thiopental sodium as with cyclopropane or ether,[49] its use is potentially dangerous in cardiac patients. On the other hand, it is the best of the long-acting muscle relaxants for patients with respiratory diseases.

Tubocurarine chloride and dimethyl-ether of tubocurarine chloride are indicated when, besides muscular relaxation, ganglionic blockade is also desirable. In view of the higher incidence and severity of unwanted side-effects with tubocurarine, the use of a suitable synthetic muscle relaxant is to be preferred under other circumstances.

The systematic search for better synthetic muscle relaxants by Bovet and others has been amply rewarded. The use of these agents, especially that of succinylcholine, makes possible the production of excellent operating conditions for surgical intervention requiring good muscular relaxation. These ideal conditions can be provided by readily controllable methods with minimal interference to the homeostatic mechanism of the patient. With intelligent administration the mortality and morbidity incident to the use of muscle relaxants is very low and compares favorably with any other agent or method used on comparable groups of patients. The use of muscle relaxants in anesthesiology is a relatively recent development, and some, if not most, of the untoward effects encountered with their use could probably be ascribed not to the toxicity of the agents but to inadequacies in their administration.

SUMMARY

The pharmacology of decamethonium (syncurine®) bromide, benzoquinonium (mytolon®) chloride, gallamine (flaxedil®) triethiodide, and succinylcholine are reviewed briefly, with special reference to their mode of action at the neuromuscular junction and to their fate in the organism. With the exception of succinylcholine, the muscle relaxants are excreted mostly unchanged through the kidneys. Succinylcholine is rapidly hydrolyzed by cholinesterases to pharmacologically inactive compounds. Due to this enzymatic breakdown, when administered in a continuous intravenous drip, the intensity of muscular relaxation produced by succinylcholine was readily controllable.

The clinical application of these agents, for the production of muscular relaxation in patients anesthetized with thiopental (pentothal®) sodium–nitrous oxide–oxygen for intra-abdominal operations, is described. These compounds decreased in potency, both on a milligram and on a molar basis, in the following order: decamethonium bromide, benzoquinonium, succinylcholine, and gallamine. The potency variation on a molar basis was less than on a milligram basis. The decreasing order of the duration of action of these agents was: gallamine, benzoquinonium, decamethonium bromide, and succinylcholine. Satisfactory relaxation was obtained with all four agents. Transient apnea was observed with the use of decamethonium bromide, benzoquinonium, and gallamine in 12.4% to 21% of the patients. No apnea was encountered with succinylcholine.

Prolonged postoperative respiratory depression was seen in 1% to 2% of the patients with the use of decamethonium bromide, benzoquinonium, and gallamine. This complication was not encountered with succinylcholine. The only other side-effects encountered were moderate tachycardia and elevation of blood pressure with the use of gallamine and increased bronchial secretions with benzoquinonium. The percentage of patients reacting to stimulation at the end of the operation was 17 for decamethonium bromide, 67 for benzoquinonium, 70 for gallamine, and 58 for succinylcholine. The indications and contraindications of these synthetic muscle relaxants are discussed on the basis of their controllability, duration of action, and side-effects.

1400 Locust St. (19) (Dr. Foldes).

Prisoners of Emotional Disorders.—Few state hospitals have programs of intensive treatment comparable to that of progressive private mental hospitals. Even though our state mental hospitals are the best in the world, they are largely custodial. Eighty per cent of psychiatric patients can be returned to usefulness through intensive psychiatric treatment. It is our job to provide the readily available means to treat, and cure, these hundreds of thousands of sick people. The world shudders when it hears of a few thousand prisoners of war; today five million people in this country alone are Prisoners of Emotional Disorders, 700,000 of them in state hospitals. Unless we act, in a few years there will be a million in state hospitals—Prisoners of Emotional Disorders—victims of the strains of society; people who could not pay the Income Tax of Civilization.—William B. Terhune, M.D., Making the Most of Man, *The Journal of the Maine Medical Association*, September, 1952.

NONDEMENTING PSYCHOSES IN OLDER PERSONS

John J. Madden, M.D., Joseph A. Luhan, M.D., Leo A. Kaplan, M.D.
and
Harold M. Manfredi, M.D., Chicago

During the past several years, and after a long period of institutional isolation, psychiatry has become well established in the field of private practice. Facilities for such practice in general hospitals are widespread throughout the country and have increased public demand for psychiatric care on the same terms as care provided in physical illness. This has undoubtedly brought about certain reorientations causing physicians to adopt a more optimistic attitude toward both treatment and prognosis in many patients hitherto regarded as unfavorable candidates for intensive, short-term therapy. In the setting of a general hospital the psychiatrist often finds himself the center of strong pressures exerted by the referring physician and relatives to treat an older patient for whom he may offer only the most guarded prognosis. Under these circumstances we have had under our care in the psychiatric unit of a general hospital a series of 300 patients over the age of 45 years with no antecedent history of disabling mental illness. When first seen, many of these patients exhibited much in their behavior suggestive of organic disease of various types, including chronic brain syndromes. Ordinarily these seeming somatic alterations would invalidate a favorable prognosis and seriously weigh against an active therapy program. In retrospect it has been found that none of our 300 patients really suffered from an irreversible organic syndrome as the essential cause of the presenting behavior disturbance.

We were impressed by the heterogeneity of the presenting psychiatric disturbances in our patients. It was often difficult to classify these disorders in accordance with the standard nomenclature of disease in general use prior to 1952. Our final diagnostic grouping, sometimes strained to conform to the older nomenclature for the requirements of the hospital record librarian, is based on discharge diagnoses, occasionally revised in the light of follow-up studies and further analysis. Nearly all of our patients were observed, treated, and classified before the newer nomenclature recently compiled by the American Psychiatric Association [1] became available.

In the past most of the serious behavior disturbances occurring for the first time after the age of 45 years were lumped under the categories of involutional melancholia, psychoses with cerebral arteriosclerosis, senility, and syphilis. Schizophrenia, cyclothymic disturbances, and psychoneuroses are generally considered to make their appearance in earlier life. The newer classification gives recognition to disorders of a functional mien, irrespective of age, and minimizes the role of deteriorating organic change in their pathogenesis. The arteriosclerotic and senile psychoses are designated separately as chronic brain syndromes. A study of our records disclosed an unusual number of patients who first became mentally ill after the age of 45 years showing behavior disturbances indistinguishable from the early life classical functional syndromes of psychoneurosis, paranoid states, cyclothymic disorders, and schizophrenia (see table). Similar observations with respect to mental disorders in the involutional period had been made by Jacobi.[2]

INVOLUTIONAL PSYCHOSES

Over half of our cases represented involutional psychotic reactions, presenting a medley of basic reaction patterns, exhibiting a major theme of agitated depressive reaction with or without variations in the form of accompanying neurotic and/or paranoid features. The new diagnostic and statistical manual of the American Psychiatric Association [1] defines involutional psychotic reaction as follows: "The reaction tends to have a prolonged course and may be manifested by worry, intractable insomnia, guilt, anxiety, agitation, delusional ideas and somatic concerns. Some cases are characterized chiefly by depression and others chiefly by paranoid ideas. Often there are somatic preoccupations to a delusional degree." Henderson and Gillespie [3] have defined the symptomatology of involutional melancholia as follows: ". . . the symptoms centre round a state of anxiety and agitation, accompanied by delusions of a depressive nature, frequently hypochondriac or nihilistic. This state although common to the great majority of cases, shows all kinds and shades of variation, so that no two cases are exactly the same."

Diagnostic Classification of Behavior Disturbances in 300 Cases

Type of Reaction	No. of Cases	Percentage of Cases
Involutional psychosis	160	53.3
Psychotic depression (other types)	52	17.3
Severe neurotic reaction	31	10.3
Psychosis with cerebral arteriosclerosis	16	5.3
Paranoid psychosis	15	5.0
Schizophrenic psychosis	9	3.0
Manic-depressive psychosis	9	3.0
Toxic psychosis	8	2.7

Some cases of involutional psychoses in the beginning may be marked by intractable insomnia, particularly early morning wakefulness, as the only apparent presenting complaint. The depression characteristically is worse in the morning, as has been noted by other observers.[4]

Read before the Section on Nervous and Mental Diseases at the 101st Annual Session of the American Medical Association, Chicago, June 11, 1952.

From the Department of Neurology and Psychiatry, Stritch School of Medicine of Loyola University, and the Department of Psychiatry of Loretto Hospital, Chicago.

Some of the bibliographic references have been omitted from THE JOURNAL because of lack of space; however, they are included in the authors' reprints.

1. Committee on Nomenclature and Statistics of the American Psychiatric Association: Diagnostic and Statistical Manual: Mental Disorders, Washington, American Psychiatric Association Mental Hospital Service, 1952.

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Self-destructive trends are common; 26.8% of our patients had either (unsuccessfully) attempted or had seriously considered suicide. These patients tend to show a peculiar rigidity of outlook and stereotypy of behavior, given to repetitive utterances of apprehension and despair, and their thought processes seem mired in a rut.[5]

Palmer and Sherman [6] emphasized the frequent occurrence of paranoid trends in involutional psychoses (melancholia), finding these in 28 out of 50 patients studied. The paranoid features may be a striking characteristic of an involutional psychosis, but there must also be considerable anxious depression in the syndrome to qualify it for inclusion under the heading of involutional psychotic reaction. Paranoid reactions without significant depression occurring in the involutional age were separately classified by us as paranoid psychoses.

The age limits for this disorder are not very definite; Henderson and Gillespie [3] cite a case beginning at 38 and another at 65. The 67 cases for Hoch and MacCurdy [7] ranged in age from 39 to 69 years. The age range of our patients with involutional psychotic reactions was from 45 to 74 years. The ratio of women to men in our series was 2.1 to 1. We cannot see why a mental disorder with content typical of involutional psychoses occurring for the first time after 70 years (as in case 1), with recovery under the influence of electroshock therapy, should be excluded from this classification simply because of age. Case histories illustrating the complexity withal the essential distinctiveness of the variegated involutional psychotic reactions encountered in our series follow.

Case 1 (depressed type).—A 74-year-old married woman was admitted to the hospital with marked depression of mood associated with severe apprehension and restlessness. She frequently entertained suicidal thoughts and was markedly self-accusatory. Her illness began when her husband made plans to retire and move to a small town. She began to complain of fatigue and gastric distress, whereupon her family physician made a diagnosis of gastric ulcer. At this point she became severely depressed, convinced that she had cancer. Study of the prepsychotic personality disclosed attributes of rigidity and compulsiveness. She had accommodated to the stress of menopause and to the death of her daughter 11 years previously in a normal manner. The patient on admission was markedly dehydrated, emaciated, and in poor general condition. Supportive and restorative measures were first employed, followed by electroshock therapy (10 treatments). Recovery ensued.

Case 2 (predominantly depressive, with psychoneurotic [hysterical] features).—A 55-year-old married man became depressed shortly after selling his home eight months prior to admission. He brooded over the sale and would talk of nothing else. A progressive restriction of interests followed, until he dropped all his former social activities and could no longer carry on his business. Psychotherapeutic interviews begun four months after onset were unavailing. Two months prior to admission jerking and dystonic movements of the head and shoulders began. On admission the patient was found to be depressed in mood, but he did not express any suicidal ideas. Restlessness and anxiety were marked, and he slept poorly. There were frequent jerking and twisting movements of the neck and shoulders. No evidence of dementia or organic neurological disease was clinically determinable. Following a course of electroshock therapy, the depressive trends and dystonic movements disappeared and the patient was discharged as markedly improved.

Case 3 (with paranoid and depressive features).—A 47-year-old married woman began to exhibit psychotic behavior of an agitated, depressive, and paranoid nature six months after a hysterectomy. Shortly before admission the patient felt that she was under the surveillance of the Federal Bureau of Investigation and was obsessed with the idea that she suffered from a contagious venereal disease. In an acute fit of depression she slashed her neck, wrists, and abdomen. Earlier history described periods of transient hyperirritability and a histrionic personality make-up. Her mother had been institutionalized because of a psychiatric disorder in the involutional period. One brother committed suicide in middle age. The patient received electroshock treatment, following which there was considerable alleviation of her depressive mood with but little change in her projection attitudes.

Prior to the advent of convulsive therapy, the outlook for involutional psychoses was rather bleak. Chapman [8] reported on a series of cases observed at Elgin State Hospital during 1930 to 1935; 32% of the patients had died after an average duration of illness of three years, about the same number remained unimproved during the five year period, and marked improvement or recovery occurred in 25%. The average duration before improvement was two years, eight months. Strecker, Ebaugh, and Ewalt,[9] state: "Before the advent of shock therapy involutional melancholia was lengthy in duration. . . . The spontaneous recovery rate is about 23 to 40 per cent. The mortality by suicide and intercurrent disease is about 20 per cent, and about 25 to 32 per cent of untreated patients become chronic." Electroshock therapy has completely altered the outlook in predominantly depressive involutional psychoses, spectacular results to be expected in a substantial majority of treated cases; however, in an evaluation of the results of convulsive therapy Kalinowsky and Hoch [10] distinguished two groups: one in which depressive features predominate, with a recovery and much improved rate of 86.9%, in contradistinction to a second group of involutional psychoses with paranoid features in the ascendancy, with good results occurring in only 43.7%.

PSYCHOTIC DEPRESSIONS

In a former communication [11] concerning a smaller group from the same population as the current study, the unorthodox term "presenile depression" was used to indicate nondementing psychoses marked by depression, often with apathy, occurring for the first time after the age of 60. We have reclassified this group, transferring some cases to the category of belated involutional psychoses, leaving most of them in the classification of depressions (other types not involutional and not clearly manic-depressive) in an involutional, presenile, or senile setting. Probably these would best fit under "psychotic depressions" in the new classification.[1] The clinical symptomatology was indistinguishable from simple cyclothymic depressions encountered in younger persons and also from so-called psychoneurotic depressions of earlier life. It is difficult in these cases to determine whether exogenous or endogenous factors were of prime importance in their pathogenesis. We could not exclude subtle

6. Palmer, H. D., and Sherman, S. H.: The Involutional Melancholia Process, Arch. Neurol. & Psychiat. **40**: 762 (Oct.) 1938.

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11. Madden, J. J.; Luhan, J. A.; Kaplan, L. A., and Reidy, J. J.: Psychoses of Later Life, Illinois M. J. **100**: 129 (Aug.) 1951.

brain changes, particularly of the cerebral arteriosclerotic variety, in many of those patients, and furthermore it was difficult to properly evaluate the multiple factors of an environmental nature. As a result we were unable to determine with critical certainty which factors played the decisive role in disturbing former emotional equilibrium and personality resiliency. The symptomatology, again as in involutional psychoses, sometimes included neurotic and paranoid components, but in its essence consisted of a quiet depression. An example of this type of depression in a senile setting is the following case.

CASE 4.—A 71-year-old unmarried woman had been a schoolteacher until her retirement a few years before to accept the position of executrix of several estates. She was described by her friends as having been a gregarious, self-opinionated woman. Following a recent decrease in her salary she became progressively depressed and in a nonagitated fashion began to express concern over her future. Her sleep was disturbed. There was considerable psychomotor retardation and poverty of thought. There were seeming deficiencies in memory and ability to calculate. Hypertension (200/100) and some electrocardiographic changes suggestive of relatively serious myocardial disease were present. Ten electroshock treatments were given, followed by severe treatment confusion that subsided in two weeks, and the patient was discharged as markedly improved. A mild recurrence five months later yielded to a course of five outpatient electrical treatments, whereupon the patient remained mentally well until two and one-half years later, when she died following a cerebral hemorrhage. Routine autopsy examination revealed no destructive cerebral changes apart from the hemorrhage to account for her previous behavior disturbance.

OTHER BEHAVIOR DISTURBANCES

Severe Neurotic Reaction.—We have encountered a number of patients retaining adequate rapport with reality whom we feel have basically psychoneurotic reaction patterns that became exaggerated by involutional and/or organic factors to such a degree that psychiatric inpatient care was required. These cases were sometimes designated by us as psychoneurosis in an involutional setting tantamount to psychosis. The longitudinal history of these patients revealed occasional psychoneurotic traits and symptomatology, never formerly reaching the threshold of such severity as to disrupt a usual, normal routine of living. An example follows.

CASE 5 (neurasthenic type).—A 59-year-old married man was admitted to the hospital because of purported inability to work for a period of about five months. At the onset of his disability he was seriously ill and in bed for a week with severe upper respiratory tract infection. Following the subsidence of the acute symptoms he refused to regard himself as well and, in spite of reassurance by his family physician and encouragement from his family, continued to protest that he was unable to work. He complained of pain in the chest and insisted that if he returned to work he would become seriously ill. He remained idle at home, making frequent complaints concerning his physical disabilities and demanding so much attention that the household routine was disrupted and the economic stability of the family was threatened. On admission no significant depression or anxiety was present. He was not self-accusatory, and the only significant complaints were chest pains (without organic basis) and fear of return of illness. His premorbid personality revealed elements of dependency, insecurity, and occasional somatic complaints with tendency to depression, but these had never heretofore reached disabling proportions. He was given nine electroshock treatments with resultant marked improvement.

Psychosis with Cerebral Arteriosclerosis.—In this series there were 16 cases with a final diagnosis of psychosis with cerebral arteriosclerosis. These represent instances of quasi-organic psychosis, a term introduced by two of us (J. J. M. and J. A. L.).[12] Rothschild,[13] in a number of clinical and neuropathological studies, has considered the problem of whether the amount and situation of damage to the brain, as disclosed by anatomically demonstrable cerebral lesions associated with aging processes, could satisfactorily explain the mental symptoms in cases of psychoses with arteriosclerosis and senility. He found, especially in the arteriosclerotic group, numerous inconsistencies between the extent of the cerebral lesions and the severity of the mental symptoms—both disturbance of behavior, little demonstrable neuropathological change, and mild mental alterations with severe cerebral damage. An example of a case classified as a psychosis (predominantly hypomanic in form) with cerebral arteriosclerosis follows.

CASE 6.—A 55-year-old widow on admission was found to be markedly hyperactive, insomnic, distractable, and euphoric with momentary outbursts of depressive ideation (fear of impending death). She was oriented in all spheres but was deficient in retentive ability and knowledge of recent events. Her illness was of two months' duration and had not been associated with any particular environmental stress. Five years before she had experienced a cerebral vascular accident marked by left hemiparesis, which had practically disappeared. Neurological examination now disclosed evidence of moderate right-sided hemiparesis, and it was concluded that a more recent cerebral vascular accident may have served as a precipitating factor for her mental illness. Her mother had been a rejecting, borderline mental defective, and the patient as a result assumed household responsibilities during childhood. Her usual personality makeup was of an outgoing type, and the past history revealed that the patient had withstood severe environmental stresses. Her husband had died from tuberculosis some 15 years previously at the Elgin State Hospital, where he had been admitted because of psychosis with cerebrovascular accident. General physical examination disclosed hypertension (210/110) and electrocardiographic changes indicative of diffuse structural disease of the myocardium. Excellent recovery from her mental illness ensued, after treatment-induced confusion produced by five electroshock treatments subsided.

In these cases classified as arteriosclerotic in origin, in some depressions in a presenile setting, and occasionally in involutional psychoses there may occur symptoms ordinarily considered to indicate dementia (disorientation, and defects in recent memory, retention, calculation, and judgment), which may disappear on alleviation of the psychotic picture by means of short-term intensive therapy. Such pseudodementia was noted in 10% of all our cases. None of these showed witzelsucht, aphasia, or epileptiform seizures. Illustrative of seeming dementia complicating a recurrent depressive reaction is the following case.

CASE 7.—A 63-year-old woman was admitted because of three weeks' history of marked anxiety and depression, insomnia, neglect of person, fatigue, buzzing in the ears, and visual hallucinations (seeing her dead parents walking about without their heads). She was disoriented for time and place and showed tion. Past history revealed her to have been a socially restricted, marked deficiencies in recent memory, retention, and calculadependent, and insecure person who was adequately adjusted until the age of 47, when she was admitted to a rest home for

12. Madden, J. J., and Luhan, J. A.: The Feasibility and Advantages of Outpatient Electroshock Therapy for the Mentally Ill, M. Clin. North America **29**: 165 (Jan.) 1945.

13. Rothschild, D.: Neuropathologic Changes in Arteriosclerotic Psychoses and Their Psychiatric Significance, Arch. Neurol. & Psychiat. **48**: 417 (Sept.) 1942. Pathologic Changes in Senile Psychoses and Their Psychobiologic Significance, Am. J. Psychiat. **93**: 757 (Jan.) 1937.

treatment of a mild depressive reaction. She was given electroshock treatment two years prior to admission because of depressive psychosis and remained well until the present illness, which had been precipitated by the death of a relative. There was evidence of well-marked generalized arteriosclerosis. In spite of this and the seeming dementing component of her mental illness, the patient was given electroshock treatment and made a remarkable recovery after seven treatments. She became oriented and at discharge manifested no disturbance in retention, recent memory, and ability to perform arithmetical calculations.

Paranoid Psychoses.—Under paranoid psychoses we have classified reactions indistinguishable from paranoid states encountered in younger persons, with insignificant depressive content developing in persons who were dissatisfied, suspicious, querulous, and argumentative prior to their breakdown. It is likely that, because of age incidence and the availability of the classification of involutional paranoid psychosis, other psychiatrists would have classified some of these with the cases of involutional psychoses. An example of a paranoid psychosis from our case material follows.

CASE 8.—A 49-year-old married man manifested acute paranoid symptoms three weeks prior to his admission to the hospital. As a policeman he had arrested for speeding a cab driver with a criminal record and influential friends. This driver obtained dismissal of the charge, following which the patient became fearful of his life. The patient was apprehensive, somewhat overactive, but was not depressed. While in the hospital he was combative and reacted with suspicion toward the ward personnel and patients. He felt that some of the patients in the ward were in league with his persecutors and that dire harm was impending. The prepsychotic personality was predominantly of an extrovertive type, with some attributes of obstinancy and suspicion. The patient received a total of 17 electrical treatments on an inpatient basis and 30 more treatments as an outpatient. The treatment period lasted seven months. He made a good recovery.

Schizophrenic Psychoses.—It is interesting that perfectly typical schizophrenic symptomatology, particularly of the catatonic type, may develop for the first time after the age of 45 years. Our eight patients ranged in age of onset from 45 to 58 years. Five were women. An example of a late appearing acute catatonic schizophrenic reaction follows.

CASE 9.—A 47-year-old married woman was admitted in a state of acute catatonic excitement. She became markedly withdrawn following the death of her father and brother (one week apart) three weeks previously, and two days prior to admission she had become acutely excited. On entrance to the hospital she was combative, hyperactive, out of contact, vividly hallucinating, delusional, and disoriented for time. She was placed under restraint and heavy sedation without improvement, and finally an electroshock treatment was given. Because of her state of exhaustion and general physical depletion she was a poor candidate for shock therapy and exhibited alarming symptoms (prolonged pulselessness and apnea) following the electrically induced convulsion. In spite of this immediate unfavorable reaction to treatment, her condition markedly improved without further electrical therapy and she was discharged from the hospital two weeks after the single treatment. This person remained well until one year later when she again became acutely psychotic. She had been arranging various commemorative services at the time. During her second admission she was negativistic and withdrawn and would alternate between catatonic stupor and excitement. She exhibited Jacksonian-like seizures involving the left extremities, but careful neurological examination, including spinal puncture and air studies, revealed no evidence of space occupying intracranial lesion. She was given four electroshock treatments and discharged in a short time as markedly improved. The past history and family history were negative for predisposing factors.

Toxic and Manic-Depressive Psychoses.—Just as persons who are handicapped psychologically (in personality make-up or by unusual situational strains) seem more vulnerable to arteriosclerotic psychosis, so senile and arteriosclerotic persons may be more vulnerable to toxic influences,[14] as was illustrated by the development of toxic confusional reactions to bromide, barbiturate, and thiocyanate medication. We had eight cases of toxic psychosis in this series.

Manic-depressive psychosis, contrary to general belief, may begin in the senium. We had eight instances of manic-depressive psychosis appearing for the first time in the age range of 46 to 77 years. The following case deserves special mention.

CASE 10.—A clergyman was 77 years old when first seen. He was admitted to the hospital because of hypomanic behavior characterized by elevation of mood, overactivity, facetiousness, and marked sleeping difficulty. He had not been subject to any unusual environmental stress except that a bowel resection and colostomy had been performed five years previously for a possible neoplasm. His previous personality was described by his friends as outgoing, but no wide mood swings were reported, and he had achieved considerable eminence in his profession. Since his first admission, in April, 1949, the patient has had four readmissions for treatment of the same symptoms. He responded well on each occasion to electrical treatment but the remissions had not lasted longer than seven months. Between attacks he was able to discharge his professional obligations without difficulty. There were no progressive changes in his intelligence, memory, or judgment indicative of dementia. At this time (May, 1952) our 81-year-old former patient, in a state of remission, appears much younger and more sprightly than his years.

CONCLUSIONS

The experience of short-term therapy in a general hospital psychiatric facility and a closer inspection of the character of the behavior disturbance in older patients has been surprisingly revealing. In private psychiatric practice organic dementia of an irreparable nature is less frequent than is generally supposed. These observations closely coincide with those made by Gallinek,[15] whose gratifying experience with electroshock therapy in patients whose symptoms strongly suggested chronic brain syndrome closely paralleled ours. We conclude with him that organic factors play an imponderable but not a discouragingly significant role.

A relatively high percentage of our patients made excellent recoveries following short-term care. In this group no long-term follow-up investigation has been conducted, but in a previous study [11] of a smaller similar group sustained remissions were found to occur in about two-thirds of the patients. The average length of hospitalization was less than four weeks.

The requirements of a somewhat inflexible nomenclature and the ominous specter of tradition seem to have obscured our recognition of disturbances easily identified in younger patients. We feel strongly that the entire gamut of psychiatric disturbances may be encountered for the first time in patients over the age of 45 years.

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PROPHYLAXIS AGAINST GROUP A STREPTOCOCCAL INFECTIONS IN RHEUMATIC FEVER PATIENTS

USE OF NEW REPOSITORY PENICILLIN PREPARATION

Gene H. Stollerman, M.D., Irvington-on-Hudson, New York
and
Jerome H. Rusoff, M.D., New York

There are two effective methods now available for the prevention of rheumatic fever or its recurrences. Prompt and vigorous treatment of the initiating streptococcal infection with one of the antibiotic drugs may prevent the complication of rheumatic fever, or the maintenance of continuous antibiotic therapy in the rheumatic subject may prevent recurrences by affording protection against infection by group A streptococci.[1] Penicillin promises to be the antibiotic of choice for the prevention of rheumatic fever by either of the above methods for several reasons: its action is bactericidal rather than bacteriostatic [2]; the streptococcal pharyngeal carrier state is eliminated most effectively by treatment with adequate doses of penicillin [3]; strains of group A streptococci resistant to penicillin have not emerged, despite the widespread use of this drug [4]; and fatal or serious toxic reactions are relatively rare.

The problem of employing penicillin as a prophylactic agent is largely a practical one. Current methods for maintaining continuous prophylaxis with penicillin involve oral administration of relatively large doses, once to three times daily, with the patient in the fasting state.[1e] The success of such treatment depends largely on the patient's strict adherence to this regimen without interruption. In addition, only a fraction (about one-fifth) of the dose of penicillin administered is absorbed [5] and the oral route is, consequently, costly and wasteful. Parenteral administration of available repository procaine penicillin preparations has not been employed for continuous prophylaxis because of the frequency with which injections would be required. If, however, penicillin could be maintained in the tissues for protracted periods by means of single injections given at infrequent intervals, parenteral administration should prove economical and practical.

Treatment of the initiating streptococcal pharyngitis with penicillin to prevent the subsequent development of rheumatic fever usually requires repeated intramuscular injections or large orally administered doses of penicillin for about 10 days.[6] In routine medical practice, bacteriological confirmation of the streptococcal etiology of pharyngitis is rarely obtained, and penicillin often is not administered for an adequate period. There would, therefore, be considerable practical advantage in a preparation with which successful treatment of streptococcal respiratory infection could be obtained by a single intramuscular injection.

Recently, a new repository penicillin compound was synthesized that provides detectable levels of penicillin in the blood of humans for prolonged periods following single intramuscular injections.[7] N,N′ dibenzylethylenediamine dipenicillin G ("bicillin") is a sparingly soluble salt prepared by the chemical combination of two molecules of penicillin G with one molecule of dibenzylethylenediamine base.[8] Its solubility is about 200 units of penicillin per milliliter of water at 40 C. It is stable in the dry, powdered state or in aqueous suspension for at least two years. Its toxicity for experimental animals is similar to that of procaine penicillin.[9]

The present study was undertaken to evaluate the efficacy of administration of this compound over protracted periods to children with rheumatic fever. The data presented indicate that low concentrations of penicillin may persist in the serum of a patient for as long as four weeks following a single intramuscular injection and that single injections of this compound are usually effective in eliminating group A streptococci from the pharynx.

METHOD AND MATERIAL

"Bicillin" was administered as a prophylactic agent to a group of 135 children who were known rheumatic subjects, who were admitted to Irvington House during the period July 1, 1951 to May 1, 1952. At the time of admission, patients were in the active stage of rheumatic fever or were convalescing from a recent attack of the disease. They ranged in age from 6 to 14 years. One of the following dose schedules was employed: 300,000 units given intramuscularly once weekly; 600,000 units given once every two weeks; or 1,200,000 units given once a month. In the early part of the study, the material was administered as an aqueous suspension of the dry powder in a concentration of 300,000 units per milliliter. Later

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Kenji Nogaki and Lucille Bralower gave technical assistance in this study.

These studies were supported in part by grants from the Masonic Foundation for Medical Research and Human Welfare and Wyeth, Inc.

Because of space limitations, some of the bibliographic references have been omitted from THE JOURNAL and will appear in the authors' reprints.

Fellow in Rheumatic Fever, New York State Department of Health (Dr. Rusoff); from Irvington House, Irvington-on-Hudson, and the Department of Medicine, New York University College of Medicine, New York (Drs. Stollerman and Rusoff).

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in the study, a more concentrated preparation containing 600,000 units per milliliter suspended in a polyvinylpyrrolidone vehicle was employed. Most patients received repeated injections at regular intervals during hospitalization, except in instances in which the effects of a single injection were studied. A total of 1,753 injections were administered to 135 children and 8 adults. The duration of prophylaxis was as follows: 33 children received regular injections for 8 to 10 months, 31 were treated for 4 to 8 months, 15 for 2 to 4 months, and 56 for less than 2 months. Observations were made on the magnitude and duration of serum concentrations of penicillin following injections, the response of group A Streptococcus carriers, the effect on the pharyngeal flora, penicillin resistance of Streptococcus viridans following prolonged treatment, local and systemic tolerance of the drug, and the incidence of recurrence of rheumatic episodes.

Injections were made with a 20 gage needle deep into the upper outer quadrant of the buttock. Serum levels of penicillin were determined by the cup plate method employing Sarcina lutea as the test organism.[10] This method was selected because of its sensitivity in detecting small amounts of penicillin in serum. The strain of Sarcina lutea employed and penicillin G of standardized unitage were obtained from the United States Food and Drug Administration. Serum samples obtained more than two weeks after an injection that were found to contain detectible amounts of penicillin were spot-checked by treatment with penicillinase to assure the specificity of the inhibition of the test organism. Serum that could not be assayed within 24 hours of the time blood was drawn was frozen and stored at –20 C. to prevent deterioration of penicillin. Throat cultures were obtained at weekly intervals from all patients. Beta hemolytic streptococci were isolated by direct inoculation in 5% sheep blood agar. In certain instances isolation was accomplished also by direct inoculation in beef heart infusion broth containing 5% rabbit blood. Attempts were made to group and type all strains of beta hemolytic streptococci by standard methods.[11] Penicillin sensitivity of organisms was determined by a tube dilution method employing a strain of Staphylococcus aureus H as a standard reference.[10] Antistreptoylsin-O determinations were performed by a modification of Todd's method.[12]

Patients were examined immediately after and 24 hours after injections for evidence of local tenderness and inflammation. Hemoglobin level and sedimentation rate determinations, white blood cell counts, and urinalyses were performed at weekly intervals in patients during the acute stage of rheumatic fever and monthly during convalescence. Blood nonprotein nitrogen and sugar level determinations were performed in 10 patients who had been receiving regular injections of "bicillin" for six months.

RESULTS

Penicillin Levels.—Following intramuscular injections of 300,000 units of "bicillin," serum levels of penicillin were consistently low, rarely exceeding 0.2 units per milliliter, but its presence persisted in the serum for one week in 71% of the patients. Seven days after subsequent weekly injections, penicillin was detectable at low levels (0.02 to 0.09 units per milliliter) in the serum of almost all patients studied (table 1). The average daily serum level during the 16 weeks of this course was 0.06 units per milliliter. The patients' weights varied from 49 to 137 lb. (22.2 to 62.1 kg.); the average weight was 78 lb. (35.4 kg.).

Injection of 600,000 units of "bicillin" was followed by the appearance of penicillin in the serum of all patients tested for as long as 12 to 14 days after each injection (table 2). This larger dose resulted in prolongation of the period during which penicillin persisted in the serum rather than in significant elevation of penicillin concentration.

Ten patients received 1,200,000 units of "bicillin" intramuscularly in divided doses of 600,000 units, administered simultaneously in each buttock. The percentage of patients in whom detectable serum levels of penicillin appeared was as follows: at the end of one

TABLE 1.—*Serum Levels of Penicillin in Children Receiving Intramuscularly 300,000 Units of "Bicillin" Weekly*

	1st Week			2nd Week			3rd Week			4th Week			8th Week	16th Week
No. of days after last injection	1	4	7	1	4	7	1	4	7	1	4	7	7	7
No. of patients *	25	5	28	24	6	28	18	5	23	20	5	24	32	26
Range (units/ml.)	0.02 to 0.14	0.03 to 0.05	0.02 to 0.06	0.04 to 0.24	0.03 to 0.07	0.03 to 0.05	0.04 to 0.12	0.04 to 0.06	0.03 to 0.08	0.03 to 0.12	0.03 to 0.06	0.03 to 0.07	0.02 to 0.09	0.05 to >0.21
Average (units/ml.)	0.06	0.03	0.03	0.07	0.05	0.04	0.08	0.05	0.04	0.07	0.04	0.04	0.05	0.10
Percentage assayable (>0.02 units/ml. by Sarcina lutea method)	92	100	71	100	100	93	100	100	100	100	100	100	100	96

* Number of patients sampled from a group of 40 who were treated for 16 weeks.

TABLE 2.—*Serum Levels of Penicillin in Children Receiving 600,000 Units of "Bicillin" Intramuscularly Every Two Weeks*

	2nd Week			4th Week			6th Week			8th Week			12th Week
No. of days after injection	7	9	12	7	10	14	7	9	12	7	10	14	14
No. of patients *	8	5	4	13	3	3	11	5	4	8	3	4	8
Range (units/ml.)	0.03 to 0.07	0.03 to 0.05	0.03 to >0.21	0.03 to >0.21	0.03 to 0.07	0.09 to 0.15	0.05 to >0.21	0.05 to 0.09	0.04 to 0.06	0.05 to >0.21	0.05 to 0.13	0.04 to 0.08	0.04 to >0.21
Average (units/ml.)	0.04	0.04	0.09	0.08	0.05	0.12	0.12	0.07	0.05	0.08	0.09	0.06	0.08
Percentage assayable (>0.02 units/ml. by Sarcina lutea method)	100	83	100	100	100	100	100	100	100	87	100	100	100

* Number of patients sampled from a group of 43 who were tested for 12 weeks.

10. Methods in Medical Research, edited by V. R. Potter, Chicago, Year Book Publishers, Inc., 1948, vol. 1: Assay of Antibiotics, edited by H. Welch, p. 25.

week, 100%; at the end of two weeks, 89%; at the end of three weeks, 89%; and at the end of four weeks, 67% (table 3).

Seventeen patients each received 1,250,000 units of "bicillin" in a volume of 2.5 ml. as a single intramuscular injection. This group included four adults. Penicillin

TABLE 3.—*Serum Levels of Penicillin Following Intramuscular Injection in Two Sites of 1,200,000 Units of "Bicillin"*

No. of days after injection	1	7	14	21	28	35	40
No. of patients	10	10	9	9	9	8	8
Range (units/ml.)	0.03 to >0.21	0.02 to 0.13	0.06 to 0.14	0.04 to 0.09	0.03 to 0.06	0.03 to 0.05	0.04
Average (units/ml.)	0.10	0.06	0.08	0.06	0.04	0.04	0.0
Percentage assayable (>0.02 units/ml. by Sarcina lutea method)	100	100	89	89	67	50	25

levels in serum samples obtained at weekly intervals were comparable to those in the preceding group. At the end of three weeks all patients had assayable penicillin levels, and after four weeks the serum of 75% of the patients continued to show small but detectable amounts of penicillin (table 4). Because of the apparent persistence of penicillin in these patients' serum for such unusually long periods at levels often at the lower limits of the sensitivity of the method employed, serum samples obtained more than two weeks after injections were checked by treatment with penicillinase to assure the specificity of the inhibition of the test organism. Bacterial inhibition in all samples tested was shown to be destroyed by the action of penicillinase. In addition, penicillin levels assayed in 10 serum samples obtained four weeks after injection of 1,250,000 units of penicillin were independently confirmed by another laboratory.* The height and duration of the penicillin level was not affected by the activity of the patient. This was shown by a comparison of a group of children confined to bed with those permitted full convalescent activity.

Effect of Treatment on Group A Streptococci.—During the study, 10 patients admitted to Irvington House and 3 adult members of the staff were found to be carrying group A streptococci in the pharynx. One patient had clinical pharyngitis due to this organism. Throat cultures were made daily for one week following injection

TABLE 4.—*Serum Levels of Penicillin Following Intramuscular Injection in One Site of 1,250,000 Units of "Bicillin"*

Period after injection	1 hr.	7 days	14 days	21 days	28 days	35 day
No. of patients	10 *	17 †	15 †	16 †	16 †	16 †
Range (units/ml.)	0.04 to 0.16	0.04 to >0.21	0.03 to >0.21	0.03 to 0.15	0.03 to 0.09	0.03 to 0.05
Average (units/ml.)	0.09	0.11	0.09	0.07	0.05	0.03
Percentage assayable (>0.02 units/ml. by Sarcina lutea method)	100	100	100	100	75	81

* Includes 3 adults.
† Includes 4 adults.

of penicillin and weekly thereafter. Group A streptococci could not be cultured from any patient's throat 24 hours after injection of "bicillin" (table 5). One patient (C. G. S.) showed a bacteriological relapse four days after receiving an injection of 600,000 units. The organism isolated was found to be sensitive to 0.02 units of penicillin. A subsequent injection of 1,200,000 units was followed by the disappearance of the organism from this patient's throat within 24 hours. Subsequent throat cultures remained negative for streptococci.

Routine weekly throat cultures were negative for group A streptococci in all but one of the patients who received regular prophylactic injections of "bicillin" during the period of study. This patient (P. W.) had been receiving 600,000 units of "bicillin" every two weeks for 15 weeks at the time she was found to be carrying type 19 group A streptococci. This organism was sensitive to 0.01 units of penicillin. At the time the positive throat culture appeared, the patient's serum contained 0.06 units of penicillin per milliliter. Previous throat cultures had been negative. Her last injection had been administered eight days previously. The organism was eliminated by an additional injection of 1,200,000 units and failed to reappear in her throat when the regular prophylactic regimen was resumed. There was no change in her antistreptolysin-O titer following this episode. None of the patients treated showed a rise in antistreptolysin-O titer.

TABLE 5.—*Effect of Intramuscular Injections of "Bicillin" on Group A Streptococcus Carriers*

Patient	Age, Yr.	Type	Dose, Units	Time Required for Disappearance of Organism, Days	Day of Relapse	Weeks Followed
R. D.	6	6	300,000 once weekly	1	0	35
W. W.	8	Undetermined	300,000 once weekly	1	0	22
M. B.	22	Undetermined	600,000 every 2 wk.	1	0	11
P. W.*	7	19	1,200,000 followed by 600,000 every 2 wk.	1	0	10
D. D.†	23	18	600,000 once	1	0	14
B. R.	61	23	600,000 once	1	0	12
B. B.	12	Undetermined	600,000 once	1	0	12
A. C.	47	Undetermined	600,000 once	1	0	10
R. A.	11	18	600,000 once	1	0	7
R. M.	9	18	600,000 once	1	0	6
F. G.	10	Undetermined	600,000 once	1	0	4
C. G. S.‡	6	Undetermined	600,000 once	1	4	2
		Undetermined	1,200,000 once	1	0	4
C. T. S.	7	5	600,000 once	1	0	4

* A positive culture developed in this patient while she was receiving 600,000 units of "bicillin" every two weeks.
† This patient had clinical pharyngitis when treatment was started.
‡ Bacteriological relapse occurred in this patient four days after disappearance of the organism.

Effect on Pharyngeal Flora.—There was no noticeable change in the pharyngeal flora of patients receiving regular injections of "bicillin." The usual saprophytic gram-positive and gram-negative organisms were found with similar frequency before and during penicillin prophylaxis. There was no increase in the incidence of monilia in the throat or stools in 77 patients receiving regular injections of penicillin.

The penicillin resistance of 27 strains of Streptococcus viridans isolated from the pharynx of 27 patients who received "bicillin" regularly for six months or more was determined. This was done because of the possibility that prolonged administration of penicillin might result in the selective growth of strains of nonhemolytic streptococci resistant to penicillin and thereby constitute a potential threat of the development of subacute bacterial endocarditis that would not be amenable to therapy with penicillin.

* Dr. Stanley S. Schneierson of the Chemotherapy Laboratory, Mount Sinai Hospital, New York, did the independent laboratory determinations.

The penicillin resistance of the strains tested ranged from 0.01 to 0.5 units (table 6). The penicillin resistance of all these organisms is well within range of the vitro sensitivity of strains encountered in cases of subacute bacterial endocarditis that usually respond to penicillin therapy.[13] The penicillin sensitivity of these strains is compared in table 6 with the sensitivity of those isolated by Krumweide [14] from patients receiving penicillin orally, 100,000 units daily, for six months. Nonhemolytic streptococci isolated from patients receiving "bicillin" were slightly less resistant than those isolated from patients receiving penicillin orally but were somewhat more resistant than those isolated from a control group (table 6). It may be of some interest that 77 dental extractions were performed on 38 patients receiving regular injections of "bicillin" during this study. In none did subacute bacterial endocarditis develop.

Local and Systemic Tolerance to "Bicillin."—Intramuscular injection of "bicillin" was usually followed by moderate burning and discomfort lasting several minutes. Several hours later, deep muscle soreness often developed and persisted for about 24 hours. This reaction was rarely severe enough to limit activity of the patient. Local redness and swelling was encountered three times in a total of 1,753 injections administered. In some patients deep induration and tenderness at the site of injection was apparent for 24 to 48 hours. Firm, nontender subcutaneous nodules, which persisted for several weeks, developed at the site of injection in 3 of the 143 patients treated. Biopsy of one of these nodules showed on microscopic section a central area of fat necrosis with surrounding granulomatous reaction and numerous multinucleated giant cells. Except for the occasional occurrence of these local reactions, most patients tolerated repeated injections well for periods exceeding nine months.

TABLE 6.—*Penicillin Resistance of Nonhemolytic Streptococci Isolated From Patients Receiving Penicillin Prophylaxis for Six Months*

Groups Studied	No. of Strains Isolated	No. of Children Studied	Strains Inhibited by Penicillin (% of Total) 0.01-0.06 Unit Per Cc. of Medium	0.12-0.25 Unit Per Cc. of Medium	0.5 Unit Per Cc. of Medium	1.0 Unit Per Cc. of Medium
"Bicillin" Group:						
Given 600,000 units intramuscularly every 2 weeks	27	27	37	52	11	0
Penicillin Group:						
Given 50,000 units orally twice a day (E. Krumweide,[14] 1949)	46	9	8.7	52.1	30.5	8.7
Control Group:						
(E. Krumweide,[14] 1949)	42	9	64.2	35.8	0	0

Penicillin hypersensitivity was encountered in four patients. In one, generalized urticaria of moderate severity developed after his 11th biweekly injection. A diffuse, papular rash was noted in a second patient after his first and sixth injections of "bicillin." In both patients symptoms appeared within 6 hours and subsided spontaneously within 72 hours. Penicillin was still demonstrable in the serum of each child four days after reactions had subsided. Injections were continued at regular intervals for additional periods of three and eight months, respectively, with no additional signs of toxicity or hypersensitivity. Generalized pruritus without skin lesions was observed in two patients. In each instance symptoms were evanescent and did not require interruption of prophylaxis. No alteration in the peripheral blood cell count, results of urinalysis, or blood urea nitrogen or blood sugar levels was noted in the patients studied.

Rheumatic Episode Recurrences.—There was no instance of a recurrence of rheumatic fever in any patient receiving regular doses of "bicillin." The significance of this observation is limited, however, since there was only one instance of a recurrence at Irvington House during the period of this study.

COMMENT

The data presented indicate that it is possible to maintain low serum levels of penicillin continuously in a high percentage of rheumatic children by relatively infrequent intramuscular injections of "bicillin." The demonstration of detectable amounts of penicillin in the serum of most patients for four weeks following the administration of 1,250,000 units of "bicillin" suggests the feasibility of maintaining continuous drug prophylaxis against recurrences by administration of single monthly intramuscular injections. It should be emphasized that the concentrations of penicillin frequently encountered (0.02 to 0.03 units per milliliter) in serum specimens obtained at long intervals after injection are at or below the limit of sensitivity of most standard tube dilution methods. The Sarcina lutea cup plate method was employed because of its sensitivity in detecting small amounts of penicillin in serum.[10] Most strains of group A streptococci are sensitive in vitro to less than 0.03 units of penicillin.[15] It is not possible, however, to accurately predict the efficiency of prophylaxis on the basis of the relation of serum concentrations of an antibiotic to the in vitro resistance of an organism.[16]

Eradication of group A streptococci from the pharynx of carriers and protection from the acquisition of the carrier state is, perhaps, a convincing test of the efficiency of a prophylactic agent. It is reasonable to assume that if both can be accomplished effectively rheumatic fever can be prevented. Single injections of "bicillin" appear to be effective in eliminating the carrier state in most but not all cases. Of the 13 patients treated, 1 required a second, larger dose to eliminate the organism, and a second patient acquired group A streptococci in her pharynx while receiving 600,000 units of "bicillin" once every two weeks. The organism was eliminated in the latter instance by an additional injection of 1,200,000 units.

The local reaction to "bicillin" is a disadvantage in the use of this compound, but, in the opinion of the authors, the degree of discomfort caused by injections is not severe enough to preclude its more extensive trial as a prophylactic agent. The apparent effectiveness of single injections of "bicillin" against group A streptococci sug-

13. Stollerman, G. H.; Roston, E. H., and Toharsky, B.: Guide to Use of Procaine Penicillin in Hospital Practice, New York State J. Med. 48: 2501, 1948.

14. Krumweide, E.: Penicillin Resistance of Non-Hemolytic Streptococci from Rheumatic Children Receiving Prophylactic Penicillin, Pediatrics 4: 634, 1949.

gests its potential usefulness in the treatment and prevention of diseases caused by other organisms, such as the pneumococcus, gonococcus, meningococcus, and Treponema pallidum, that are similarly highly sensitive to the action of penicillin.

The persistence of penicillin in the tissues for prolonged periods following injection of "bicillin" poses the theoretical objection that the development of penicillin hypersensitivity might result in severer and more protracted allergic reactions than would be encountered if penicillin were more rapidly eliminated. The brief duration of the reaction of the two patients in whom urticaria developed supports the observations of others [17] that allergic reactions to penicillin may be evanescent and do not always constitute an absolute indication for discontinuing therapy. The incidence of hypersensitivity to "bicillin" in this series is comparable to the frequency of allergic reactions encountered in parenteral use of other penicillin compounds.[18] Until further experience with the parenteral use of this compound is available, however, its administration should be restricted to patients in whom a history of penicillin hypersensitivity is carefully excluded.

SUMMARY

A total of 1,753 intramuscular injections of N,N′ dibenzylethylenediamine dipenicillin G ("bicillin") was administered to 135 children and 8 adults with rheumatic fever during a 10 month period as prophylaxis against group A streptococcal infection. Following single intramuscular injections, low levels of penicillin were detectable in the serum for unusually long periods. Single injections of "bicillin" appeared to be effective in eliminating the Streptococcus carrier state in most cases. In two patients urticarial reactions developed that persisted for only 72 hours. Local reactions were somewhat severer than those due to injections of penicillin G or procaine penicillin. "Bicillin" merits further trial as a "long-acting" prophylactic agent against rheumatic fever.

ADDENDUM

Since this paper was submitted for publication, an improved suspension of "bicillin," "injection bicillin 600," has been marketed, which produces fewer local reactions and is tolerated better than the earlier lots used in our study.

Irvington House (Dr. Stollerman).

17. Siegal, S.: Allergy to Penicillin O and Management of Penicillin Sensitivity, Am. J. Med. **11**: 196, 1951.

EPIDEMIOLOGICAL AND CLINICAL STUDY OF GRAIN ITCH

Boynton H. Booth, M.D.
and
Roland W. Jones, M.D., Indianapolis

An epidemic of human infestation by the mite Pyemotes (Pediculoides) ventricosus (Newport) has existed in the midwestern part of the United States for the past two years. Grain itch is the name commonly used to describe the pruritic eruption that the attack of this mite causes in man. Pyemotes ventricosus is ordinarily a parasite of the larvae of various grain destroying insects, and thus it is most commonly found in association with grain or straw. Agricultural workers have been chiefly affected, but industrial workers and others have been attacked through occupational or incidental exposure to infested straw. Pyemotes ventricosus was noted as abundant in the midwestern and eastern sections of the United States over 40 years ago. Schamberg [1] observed cases of grain itch in Philadelphia each year from 1901 through 1910; the source was eventually traced to mite-infested straw mattresses. A number of large epidemics of grain itch occurred among harvesters in Ohio [2] and Indiana [3] during 1908, 1909, and 1910. Rawles [3] in Indiana and Schamberg and Goldberger [4] in Philadelphia independently demonstrated in 1909 that the mite Pyemotes ventricosus was the cause of grain itch.

Recently the genus name Pediculoides has been synonymized under Pyemotes. The newer name will, therefore, be used throughout this paper. Pyemotes ventricosus apparently became uncommon in the United States after 1910 and was not a serious problem again until 1950. The scarcity of the mite during these years can be confirmed. 1. A review of the literature from 1910 through 1950 discloses only seven reports [5] mentioning the occurrence of grain itch in the United States; a total of fewer than 100 persons were affected. 2. Only one small outbreak of grain itch was reported by a group of entomologists,[6] physicians,[7] and strawboard factory personnel, some of whom had firsthand experience with the 1908-1910 midwestern grain itch epidemics. This outbreak occurred in southern Indiana in 1940.

REPORT OF AN EPIDEMIC OF GRAIN ITCH

Grain Itch in Farm Workers.—A widespread epidemic of Pyemotes ventricosus infestation of farm workers occurred in central and southern Indiana in 1950 and 1951. Harvesters exposed to wheat straw were the persons chiefly affected. Information concerning infestation of this group was obtained from entomologists, phy-

From the Department of Dermatology and Syphilology of the Indianapolis General Hospital.

This study was aided by a grant from the Charles J. Wolf Foundation for Medical Research of the Indianapolis General Hospital.

Read before the Section on Dermatology and Syphilology at the 101st Annual Session of the American Medical Association, June 11, 1952.

Some of the bibliographic references have been omitted from THE JOURNAL because of lack of space; however, they are included in the authors' reprints.

1. Schamberg, J. F.: Grain Itch (Acaro-Dermatitis Urticaroides): A Study of a New Disease in This Country, J. Cutan. Dis. **28**: 67, 1910.

2. Webster, F. M.: A Predaceous and Supposedly Beneficial Mite, Pediculoides, Becomes Noxious to Man, Ann. Ent. Soc. Am. **3**: 15, 1910.

3*a*. Rawles, L. T.: Dermatitis Ditropenotus Aureoviridis: Synonym: Straw Itch, J. Indiana M. A. **2**: 337, 1909.

4. Goldberger, J., and Schamberg, J.: Epidemic of an Urticaroid Dermatitis Due to a Small Mite (Pediculoides Ventricosus) in the Straw of Mattresses, Pub. Health Rep. **24**: 973, 1909.

6. Davis, J. J.: Personal communication to the authors.

sicians, and farmers. Davis [8] reported numerous communications from farmers, agricultural agents, physicians, and veterinarians inquiring about the condition. Many harvesters who had been bitten by Pyemotes ventricosus were observed by physicians in central and southern Indiana. Two physicians in Indiana, one in Muncie [9] and another in Terre Haute,[10] observed 145 farmers in two years suffering from grain itch. Through personal communication with numerous farmers it was learned that many were infested who did not bother to seek medical care. The number of farmers affected by grain itch was probably large, but no numerical data are available. While the epidemic occurred predominantly at harvest time, some infestation occurred throughout the entire summers of 1950 and 1951. Infested straw stored in barns was a particular source of trouble. For example, one horse breeding farm near Indianapolis had infested straw in the mow both years. Two weeks after the onset of warm weather in May the stablemen began to suffer attacks of grain itch from exposure to this straw. They continued to be harassed until the advent of cooler weather in October. Pyemotes ventricosus was found to be abundant in the straw.

Grain Itch at the Indiana State Fair.—The straw used for animal bedding at both the 1950 and 1951 Indiana state fairs was infested with Pyemotes ventricosus. These fairs, which are held annually the first week in September in Indianapolis, were attended during each epidemic year by more than one million persons.Of these persons 60% were visitors, while the other 40% helped in the operation of the fair. Attendants for the animals, including the youth group or "4-H" club members, were the persons most severely affected by grain itch. During this two year period, there were 642 persons treated for grain itch at a dispensary maintained on the fairgrounds by the American Red Cross. In the first year of the epidemic 260 infested persons received treatment and 382 the following year. Most of the patients had 200 to 300 bites. Some had systemic symptoms such as fever, malaise, vomiting, backache, secondary bacterial infection, and regional lymphadenopathy. The therapy administered at the dispensary was a bath followed by the application of the NBIN formula.[11]

DDT (dichlorodiphenyltrichloroethane)	1%
Ethyl aminobenzoate (benzocaine)	2%
Benzyl benzoate	10%
Tween® 80 (polyoxyalkalene ether of sorbitan monooleate)	2%
Water in a quantity sufficient to make	100%

If there was secondary bacterial infection, 300,000 units of penicillin was given by intramuscular injection.

The grain-itch-infested "4-H" club members were treated in a separate building because of the dispensary's limited facilities. The therapy here, also, was the application of the NBIN formula with a few (less than 40) of the more severely affected persons referred to the dispensary for observation. About 1,100 of these young persons were infested by Pyemotes ventricosus in two years: 600 in 1950 and 500 in 1951.[12] Therefore, at least 1,700 persons were treated for grain itch at the Indiana State Fair in two years. It is probable that a great many more were infested, as the majority of visitors were at the fair for a shorter period than the 10 to 16 hours that is the normal period for the onset of symptoms from the bite of Pyemotes ventricosus. Pyemotes ventricosus was isolated from the straw, and its identity was confirmed by Dr. W. H. Headlee, parasitologist for the Indiana University Medical Center. The straw was supplied both years by a strawboard factory, whose superintendent was unable to designate the exact origin of the straw other than that it did come from the state of Indiana.

Grain Itch in Strawboard Factory Workers.—Strawboard factories use straw as one of the basic raw materials from which paper is prepared. There are three of these factories in central Indiana, in all of which employees were infested with Pyemotes ventricosus in 1950 and 1951. The straw, which was purchased in Indiana and neighboring states, was stockpiled during the harvest season to be used as needed during the remainder of the year. There had been no difficulty from mite infestation prior to 1950 at the strawboard factories, with the exception of a single carload of straw that one of the factories obtained from Arkansas in 1949. They noted that infested straw came from other midwestern states as well as from Indiana and that the incoming straw was more heavily infested with mites in 1950 than in 1951.

Approximately 120 men in the three factories were affected by grain itch. One factory, which had larger quantities of mite-infested straw, had almost continuous infestation of the workers during the 1950 harvest season. While the greatest numbers of mites were present on the incoming straw at harvest time, grain itch did occur periodically throughout the summer as infested straw was removed from stock. Although there was considerable unrest among the laborers, only one quit his job and only two others were affected to such an extent as to lose time from work. Pyemotes ventricosus was first isolated in this epidemic by Dr. Headlee from straw from one of these three factories.

PYEMOTES VENTRICOSUS

Insect Hosts.—Pyemotes ventricosus is a parasite of the larvae of various soft-bodied insects, and its abundance depends on the number and availability of its hosts. Two of its principal insect hosts, the Angoumois grain moth (Sitotroga cerealella [Olivier]) and the wheat jointworm (Harmolita tritici [Fitch]) have been increasing in Indiana for several years. Their increase may be attributed to several factors.

One host, the wheat jointworm, is limited in the United States to the cereal raising area east of the Mississippi River.[13] The adult insect is a small fly that lays its eggs in the wheat stalk, and hence the larvae remain in the stalk until the insects reach maturity. In the past the wheat jointworm has shown irregular cycles of both abundance and relative scarcity.[14] A cyclic decrease of its natural parasites, such as Ditropenotus aureoviridis,[6] partially explains the present abundance of the jointworm. Another factor explaining its abundance has been the harvesting of wheat by combines. Formerly many jointworms were destroyed by the mechanical trauma of threshing, but during the last decade the combine har-

8. Davis, J. J.: The 1950 Epidemic of the Straw Itch Mite, Proc. Indiana Acad. Sci. **60**: 183, 1950.

13. Metcalf, C. L., and Flint, W. P.: Destructive and Useful Insects: Their Habits and Control, ed. 3, New York, McGraw-Hill Book Company, Inc., 1951, p. 465.

vester has gradually replaced the threshing machine. With the present methods the grain is cut close to the head, thus leaving the stalks containing the jointworm larvae standing in the field. The result is that the jointworm is permitted to survive and multiply.

The second host, the Angoumois grain moth, is distributed generally throughout the United States.[13] It infests the wheat crop in the summer but overwinters chiefly in stored corn. Abundant crops in recent years resulting in the increased storage of surplus corn have been a factor in enabling the grain moth to overwinter successfully. Temperature also plays an important role in the abundance of the grain moth, which is killed by extended temperatures of 0 F (−17.7 C) or lower.[6] The average winter temperatures in central Indiana from November through February for the past few years have been as follows:

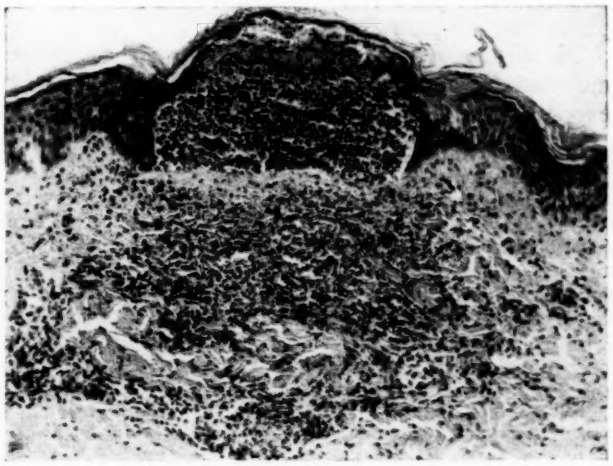
Year	Temperature	
	Fahrenheit	Centigrade
1947-1948	31.2	−0.4
1948-1949	37.8	3.2
1949-1950	36.5	2.5
1950-1951	30.5	−0.8

It may be seen that the two winters preceding the onset of the grain itch epidemic in 1950 were milder. Winter temperature analyses have shown that bad moth years have usually followed warm winters.[15] The Angoumois grain moth reached a peak of abundance in Indiana in the summer of 1950 coinciding with the greatest infestation of man by Pyemotes ventricosus. The relatively severe winter of 1950-1951 reduced the numbers of the grain moth, and there was a notable decrease in the incidence of grain itch in 1951 from the previous year.

Distribution.—The references in the entomologic literature to Pyemotes ventricosus as a parasite of various insects number in the hundreds.[16] From an analysis of this literature we believe that Pyemotes ventricosus may be world wide in its distribution, an assumption also maintained by Hunter.[17] The United States Bureau of Entomology and Plant Quarantine has isolated the mite from material sent to them from 26 different states and several islands and foreign countries. Man is attacked by the mite when the latter parasitizes insects that infest such substances as grain and straw. Epidemics of grain itch have been recorded from several European countries,[18] Africa,[19] Eastern Asia,[20] the United States,[5] and Australia.[21] Although Pyemotes ventricosus has been isolated from a majority of the states of the United States, practically all of the American epidemics of grain itch have been noted in the cereal raising district east of the Mississippi River and north of the Ohio River extending eastward to the Atlantic coast. In the present epidemic, outbreaks of grain itch occurred in several areas in central and southern Indiana. We assume that the mite has the same distribution as its present principal insect hosts, the Angoumois grain moth and the wheat jointworm. These insects infested much of the wheat crop in central and southern Indiana in 1950 and 1951, with only a tier of counties in the northern part of the state being completely free of infestation.

Biology.—Classical descriptions of Pyemotes ventricosus, its structural features and life history, have been presented by Webster [22] and Swan.[21] Normally Pyemotes ventricosus is an ectoparasite of the larval forms of many soft-bodied insects. The pupal and adult stages of these insects are less often sources of food. Man serves only as an incidental temporary host.

Both male and female mites are sexually mature at birth, which is an unusual occurrence among the Acarina.[23] The males total only a small percentage of the progeny and are usually among the first born. They remain on the mother's abdomen usually clustered about the genital orifice. As the females are delivered, fertilization by the males occurs. Soon thereafter the female mites scatter in search of food. During the birth process, which may be prolonged over 7 to 10 days and during which 200 to 300 young may be produced, the males pierce the mother-sphere thus securing a ready source of nourishment. Discovery of a new host by the female mite results in an immediate attempt at feeding. The mite possesses a needle-like mouth part, which it uses to inject an irritating substance, presumably larva, and which in man gives rise to a pruritic eruption. The mite then withdraws body fluids from the host, which are necessary for her survival and the development of young. The succession of generations varies with the temperature, new litters appearing at intervals of about one week at 90 F (32.2 C) temperatures.[22] The mites overwinter as gravid females, which deliver young after a week or so of warm weather.



Vesiculopapular lesion in grain itch.

Inasmuch as the mite can travel only short distances, its survival depends on readily available food. During high temperatures accompanied by low humidity, life cannot be sustained in the unfed female for periods longer than one day. Under reverse conditions, the female mite may survive for much longer periods without food. In extreme circumstances, the unfed male remains viable for periods up to five days.

CLINICAL MANIFESTATIONS AND PATHOLOGY

Detailed descriptions of the clinical picture is known from previous works. Schamberg [1] has given a complete account of the eruption. The characteristic, cutaneous lesion is a rosy-red wheal surmounted by a vesicle that

21. Swan, D. C: The Hay Itch Mite, J. Agr. Soc. Australia **37**: 1289, 1934.
22. Webster, F. M.: A Predaceous Mite Proves Noxious to Man, United States Agriculture Department Bulletin 118, April, 1910.
23. Pick, W., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, vol. 10, p. 503.

rapidly becomes a pustule. The wheals normally appear 10 to 16 hours after exposure and reach their maximum development in about 24 hours. The average diameter of a wheal is 0.5 cm., but variations in size occur in the same and different persons. Because of the intense pruritus, the lesions are often excoriated and secondarily infected by bacteria. The pruritus and the wheal subside spontaneously after 48 to 72 hours, but both may recur for several days if the lesions are rubbed. The number of bites depends on the abundance of the mites, the length of exposure, and the temperature. Pyemotes ventricosus is quite responsive to temperature, being most active at temperatures above 80 F (26.6 C) and showing little or no activity below 60 F (15.5 C). If exposure is prolonged and the mites are numerous, much of the body may be affected. Any part of the body may be attacked depending on the nature of the exposure. Local complications are pyoderma, eczematous reactions, and regional lymphadenopathy. Systemic symptoms that may accompany the eruption are fever, chills, malaise, headache, backache, nausea, vomiting, and asthma. Altered laboratory findings recorded include leukocytosis, eosinophilia, and albuminuria.

The histopathology of a typical urticarial lesion surmounted by a vesicopustule, biopsied 18 hours after exposure, was described as follows:[24]

> In the center of the specimen the epidermis is elevated and partially destroyed by a small, superficial pustule approximately 0.5 mm. in diameter. The stratum corneum is intact over the pustule, but in the center of it the other layers of the epidermis have been destroyed. Two or three rows of elongated cells of the rete extend along the sides of the pustule. The epidermis on either side of the pustule shows some intercellular edema but is otherwise essentially normal. The pustule is densely packed with polymorphonuclear leukocytes. The dermis is slightly edematous, but the blood vessels and lymph spaces are not markedly dilated. A perivascular infiltrate is present, which is made up of lymphocytes, histiocytes, polymorphonuclear leukocytes, and eosinophils. A Toluidine blue stain showed a few mast cells to be present, but they were not markedly increased in number either close to the pustule or at some distance from it. In the immediate neighborhood of the pustule, polymorphonuclear leukocytes and eosinophils were found scattered diffusely in the connective tissue. No parts of the mite were found in the tissue.

DIAGNOSIS AND THERAPY

The recognition of grain itch depends on the following factors. 1. An intensely pruritic eruption, of which the characteristic lesion is a wheal surmounted by a vesicle or pustule, starts abruptly. 2. The eruption, affecting families, harvesters, and other groups who have been exposed to substances that may harbor the mite, is epidemic in nature. In this country the great majority of instances of Pyemotes ventricosus infestation have occurred after exposure to wheat straw; however, infestation by Pyemotes ventricosus has been reported after contact with the following substances: tobacco, grain (wheat and barley), flour, beans, corn, peas, and linseed,[25] hay [21] and broom corn.[5g] 3. Pyemotes ventricosus is extremely difficult to detect on the human skin because of its small size and its transient stay; however, it may usually be demonstrated in straw or other contactant material without difficulty. The following methods of detecting the mite in straw have been found to be most convenient. Initially a search is made for a wheat jointworm gall, which is a hard nodule in the shaft of the straw adjacent to the joint. The gall may be broken and its contents placed on a glass slide. Microscopic examination reveals the larvae of the jointworm and its parasite, Pyemotes ventricosus, if present. Another method is to pulverize a sample of straw and then to collect the fine chaff or dust that settles. This dust should be passed through a sieve and the fine particles spread thinly on a glass surface and examined under the low power lens of a microscope. Pyemotes ventricosus may be easily identified among the debris.

Grain itch is likeliest to be confused with eruptions due to the attack of other insects. In large outbreaks of grain itch there is usually little difficulty in recognizing the cause of the trouble, but when smaller numbers of persons are infested, or isolated cases occur, one's index of suspicion may be low. The eruption may be attributed to other agents, such as chiggers, the rat mite, scabies, or other mite species. Urticaria and chickenpox may also be simulated.

The control of the insect hosts responsible for Pyemotes ventricosus is an agricultural and entomologic problem. The use of insecticides on contactant material to prevent infestation by Pyemotes ventricosus is limited by the ultimate use of the substance. It is inadvisable to use toxic insecticides on materials that may be ingested by animals or man. Pyrethrins and piperonyl butoxide were used on straw at the Indiana State Fair with good results.

The local application of miticides, sulfur, benzyl benzoate, and γ-benzene hexachloride (Kwell) has its greatest value in grain itch as a prophylactic, as the mite is only a transient parasite of man. Sulfur-impregnated clothing was recommended by Ewing.[26] Early bathing and a change of clothing after a known exposure is another effective prophylactic measure. As the eruption is self-limited when the contactant material is removed, the purpose of active treatment is to relieve pruritus and to prevent or eliminate secondary bacterial infection. Llambias and Lorenzo [27] recommended a lotion of warm water and vinegar, which was the treatment credited with giving the greatest relief by the chronically infested strawboard factory workers. Swan [28] found a saturated solution of picric acid in 90% alcohol to be effective in relieving irritation. Antipruritic lotions and ointments, collodion, and colloidal baths have also been recommended for the relief of pruritus. The NBIN formula was used extensively at the Indiana State Fair with good results being apparent. Antibiotics may be used to control secondary bacterial infection. A trial test of an antihistamine ("histadyl") in lotion form and internally was given at one of the strawboard factories and found to be of little value in grain itch.

SUMMARY

Grain itch, an uncommon disease in the United States for 40 years, occurred in the central section of the country in epidemic proportions in 1950 and 1951. Farmers, strawboard factory workers, and visitors and attendants

25. Rokstad, I.: Endemic Outbreaks of Skin Eruption Caused by Mites from Food Stuffs (Figs) and Tobacco, Acta dermat.-venereol. **24**: 113, 1943.

28. Swan, D. C.: Dermatitis Caused by a Mite (Pediculoides Ventricosus) and Its Occurrence in Australia, M. J. Australia **2**: 573, 1934.

at the Indiana State Fair were affected. In each group, mite-infested wheat straw was the contactant material responsible for dissemination of the causative organism.

The mite Pyemotes ventricosus was abundant in Indiana in 1950 and 1951. A concurrent increase in the numbers of its insect hosts supported its abundance. Four factors have contributed to the increase of these insects: (1) mild winters, (2) decrease of natural enemies of the host insects, (3) overwintering of recent large crops, thus providing shelter and food, and (4) change of harvesting methods to the use of the combine, eliminating mechanical destruction of the host insects.

The distribution of Pyemotes ventricosus, the clinical features of the disease, diagnosis, and therapeutic and prophylactic measures have been reviewed.

23 E. Ohio St. (Dr. Booth).

RESECTABLE MYCOTIC LESIONS AND ACUTELY FATAL MYCOSES

Roger D. Baker, M.D., Birmingham, Ala.

So much has been written on mycoses in the last two decades that the chief features of most of them are well known.[1] But now I wish to approach fungus infections from two angles, first from that of the surgeon and second from that of the internist, and to discuss first, resectable mycotic lesions, and second, acutely fatal mycotic disease.

RESECTABLE MYCOTIC LESIONS

The fungus disease registry that I have maintained for some years contains a number of cases in which lesions have been resected. I will now present data on these cases and pertinent information from the literature.

Amputation of a leg for mycetoma or maduromycosis is effective in eradicating the disease permanently. Resection of portions of the foot for this same condition may not prove effective. This was true in two cases of maduromycosis caused by Monosporium apiospermum. In one, a Negro man had a recurrence four years after the first resection. At the time of the first resection, in 1940, he gave a history of having had his foot stepped on by a mule 15 years previously. After a few weeks a lump developed and grew slowly. Sinuses had developed only two months previously. Roentgenograms showed a moth-eaten surface of the mesial and terminal end of the fifth metatarsal bone. The mass with incorporated extensor tendons was excised and the bone scraped. The firm, oval mass was several centimeters long and contained granules of the fungus. There was a recurrence, and additional material was removed in February, 1944. A second case, due to the same organism, had a similar recurrence 19 months after local resection. One can conclude that local resection in mycetoma may be followed by a recurrence; however, there is no danger of generalization of disease in these cases and no harm in attempting local resection initially. Amputation of the whole foot or lower leg can be done later if necessary.

Several cases are on record in which a blastomycotic larynx has been removed surgically. Usually it has been removed because the biopsy has been reported as cancer, and this error has been made because the pronounced proliferation of the stratified squamous epithelium closely simulates carcinoma. Moreover, laryngeal blastomycosis may present laryngeal changes clinically indistinguishable from laryngeal cancer. Features that should arouse suspicion of blastomycosis rather than cancer, on the part of the histopathologist, consist of microabscesses and giant cells. The periodic-acid Schiff staining method will aid in demonstrating the organisms. Laryngeal resection is not the method of choice in these cases, and evidences of blastomycosis have been discovered elsewhere in some of the reported cases in which resection had been performed.[2] In the one case of actinomycosis of the kidney, Dr. A. F. Henderson of West Palm Beach, Fla., writes, in 1952: "This man made a complete recovery from the nephrectomy. He regained his former strength and weight and has been free of illnesses since 1947."

The three patients with pulmonary cryptococcosis had rounded, solid lesions varying in size from that of a plum to that of an orange. In two cases the lesions were solitary. In the third case there were two nodules. In two cases the lesion was in the lower lobe of the right lung, and in one case in the upper lobe. The patients were in good health

Resected Mycotic Lesions

Organ	Disease	No. of Cases
Leg	Mycetoma	4
Kidney	Actinomycosis	1
Larynx	Blastomycosis	1
Lung	Cryptococcosis	3
Lung	Blastomycosis	1
Lung	Histoplasmosis	1
Lung	Coccidioidomycosis	1
Lung	Unidentified	2

9 months, 9½ months, and 4 years after operation. From these three cases one would conclude that resection of pulmonary cryptococcosis (torulosis) is effective. Perhaps resection was prophylaxis against the development of cryptococcosis of the central nervous system.

The one case of histoplasmosis in my list was described by Dr. Franz Leidler of St. Louis, who sent me sections. Lobectomy and thoracoplasty had been performed. The gross specimen showed a large cavity in the right upper lobe. Sections showed Histoplasma capsulatum in macrophages in the lining material of the cavity. The patient was in good health 15 months after operation. Last year Hodgson, Weed, and Clagett reported on two patients

From the Department of Pathology, Medical College of Alabama.

Read before the Section on Pathology and Physiology at the 101st Annual Session of the American Medical Association, June 10, 1952.

1. Conant, N. F., and others: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1944. Baker, R. D.: Fungus Infections, in Pathology, Anderson, W. A. D., editor, St. Louis, C. V. Mosby Company, 1948, chap. 16.

2. Ferguson, G. B.: North American Blastomycosis: A Review of the Literature and a Report of 2 Cases Primary in the Larynx, Laryngoscope **61**: 851-873 (Sept.) 1951.

with pulmonary histoplasmosis treated by lobectomy.[3] The patients were well more than two years after operation in one case and six months after operation in the second case. They write: "In view of our experience with two cases in which lobectomy was performed, a careful search was made to determine whether in other cases similar treatment might have been used. Of the 65 cases of pulmonary disease, in only 11 was the disease confined to one lung, but in only three of these would it appear from the report that surgical resection could have been attempted, since in the remaining cases the patients had evidence of histoplasmosis elsewhere in the body or had complications that would have prevented such a procedure. This merely reemphasizes the impression that patients who could be treated by this means probably will remain rare."

The one case of resected blastomycosis of the lung that I have registered was that of a woman operated on at Duke Hospital in 1944. Biopsy of the spine at a later date showed blastomycosis. In commenting on three cases of blastomycosis of the lung with resection that he observed, Dr. Julius Wilson of New Orleans writes: "It seems to us that surgical resection is the treatment of choice, if it can be performed before there is involvement of the chest wall." Dr. W. C. Sealy of Durham, N. C., writes concerning pulmonary resections on patients with blastomycosis: "One had an upper lobectomy, and the other a pneumonectomy. One case has been followed now for one year and the other for approximately eight months. Both are doing well thus far and are now back to full activity." Thus there appears to be a real place for resections in pulmonary blastomycosis.

The one case of resected pulmonary coccidioidomycosis in my registry had a cystic lesion in the left upper lobe 2.5 cm. in diameter. Greer, Forsee, and Mahon, reporting in 1949 on the surgical management of pulmonary coccidioidomycosis in focalized lesions, indicate that 13 patients had been treated.[4] Four patients with focalized granulomatous lesions had been treated satisfactorily by wedge resection of the diseased portion of the lung. They feel that these lesions should be removed in order to rid the patient of a possible source of dissemination and in order to rule out the possibility of a more malignant process, which might have an identical roentgenologic appearance. Coccidioidal cavities were removed by lobectomy in nine cases. They believed that lobectomy should be reserved for those patients who have distressing symptoms over a period of many months. In March, 1952, Dr. Forsee wrote me: "We have had no reason to alter this opinion in our continued experience which probably totals 35 patients." Cotton and Birsner conclude, on the basis of a series of 30 cases, that surgical treatment in pulmonary coccidioidomycosis can be used to prevent death, is effective in arresting the disease process, and does not cause dissemination of the disease.[5]

In my registry series two cases of unidentified fungus infections of the lungs were treated by lobectomy. In one case the fungus was found in the thick fibrous wall of a cavity and the possibility of a saprophytic growth in an old tuberculous cavity was considered. In the other case there was a bronchiectatic saccular cavity with similar, probably saprophytic, growth. In these cases there was no other focus in the body and the fungus was completely removed from the body. Finally, mention should be made of the possibility of eradicating small cutaneous lesions of blastomycosis or chromoblastomycosis by surgical excision. Furthermore, in all of the deep mycoses one should bear in mind the desirability of early diagnosis and chemotherapy, so that surgical procedures do not become necessary. Actinomycosis, nocardiosis, and blastomycosis might be mentioned in this respect.

ACUTELY FATAL MYCOTIC DISEASE

In general, mycotic diseases are chronic. This fact gives added interest to acutely fatal mycotic disease, which may be confused with acute infectious disease of bacterial or viral nature. Two mycoses are notable, namely, mucormycosis and blastomycosis. Mucormycosis is the most acutely fatal mycosis known. The duration of the disease has been brief, a matter of days. In five cases studied at autopsy, the duration since onset of signs was 2, 2, 3, 5, and 10 days.[6] Unfortunately, Mucor fungi have not been cultured in any of the reported cases, because the tissues were fixed before the need of cultures was realized. The appearance of the fungus in microscopic sections strongly suggests Mucor, for there are large, branching hyphae with absent or rare septa. Thus the designation mucormycosis is probably appropriate. The disease can develop, apparently, only in the presence of some factor that reduces resistance to invasion of the body by this fungus, because, of six autopsy cases, all had diabetes mellitus. The ages were those of adulthood with the exception of one patient. There was an alcoholic bout mentioned in the history of two patients. The portal of entry appears to be the nose and nasal accessory air sinuses, with spread of the fungus to the orbit and to the brain. Orbital cellulitis with periorbital swelling and diabetic coma develop. The fungus was demonstrated in the meninges and brain in all six patients, the orbit in three, the bulbus oculi in two, ethmoids in two, nares in one, lungs in two, and bronchi in one. The fungus produces acute inflammation and necrosis. The latter may be, in part, due to vascular thrombosis, because the blood vessel walls are permeated by large numbers of fungus filaments. The six cases had been reported from various parts of the United States, including Maryland, Pennsylvania, and Texas. Since the Mucor fungus is a common laboratory contaminant, the diagnosis of mucormycosis should be made reluctantly clinically and only when the evidence is overwhelming.

Systemic blastomycosis is usually of many months' duration. Moreover, it usually presents extrapulmonary lesions in bones or subcutaneous tissues, which make

3. Hodgson, C. H.; Weed, L. A., and Clagett, O. T.: Pulmonary Histoplasmosis: Summary of Data on Reported Cases and a Report on 2 Patients Treated by Lobectomy, J. A. M. A. **145**: 807-810 (March 17) 1951.

4. Greer, S. J.; Forsee, J. H., and Mahon, H. W.: The Surgical Management of Pulmonary Coccidioidomycosis in Focalized Lesions, J. Thoracic Surg. **18**: 591-604 (Oct.) 1949.

5. Cotton, B. H., and Birsner, J. W.: Surgical Treatment in Pulmonary Coccidioidomycosis: Preliminary Report of 30 Cases, J. Thoracic Surg. **20**: 429-442 (Sept.) 1950.

6. Baker, R. D., and Severance, A. O.: Mucormycosis: With Report of Acute Mycotic Pneumonia, abstracted, Am. J. Path. **24**: 716 (May) 1948. LeCompte, P. M., and Meissner, W. A.: Mucormycosis of the Central Nervous System Associated with Hemochromatosis: Report of a Case, ibid. **23**: 673-677 (July) 1947. Gregory, J. E.; Golden, A., and Haymaker, W.: Mucormycosis of the Central Nervous System: A Report of 3 Cases, Bull. Johns Hopkins Hosp. **73**: 405-419 (Dec.) 1943.

diagnosis less difficult. I have recently studied at autopsy a case of fatal blastomycosis, of only 20 days' duration, without extrapulmonic lesions.

A 41-year-old white seamstress was treated for cough, fever, and pain in the chest. Since there was no favorable response to antibiotics and sulfonamides, she was brought to a hospital on the 11th day after onset of symptoms. The signs were those of bilateral pneumonia in an obese woman, with high fever (104.2 F) and a high white blood cell count (17,350), predominantly (78%) of polymorphonuclear cells. Roentgenograms indicated bilateral pneumonia. Sputum smears revealed many gram-positive cocci in clusters and many yeast forms, which were thought to be fortuitous. A blood culture was positive for Staphylococcus albus hemolyticus. Chloramphenicol, penicillin, and aureomycin were given during the course of the disease, without favorable response to therapy at any time. The day before death the cough became productive of large amounts of blood-tinged sputum and cyanosis developed. Death occurred on the 20th day of the disease. At autopsy the lungs were many times heavier than normal. Sectioning presented yellowish-white, nodular consolidations involving both lungs, with greatest involvement of the right lower lobe, and with a greater tendency to involve hilar rather than apical regions. The cut surfaces exuded pus, but no abscesses were present. Pus swabbed from the cut surface of the lung showed numerous thick-walled organisms of Blastomyces dermatitidis, and the organism was grown in culture. In microscopic sections of the lungs the blastomycetes showed as thick-walled organisms, some of which were budding. The staphylococci were merely culturable contaminants. Blastomycosis was found only in the lungs.

The most acute case of which I had personal knowledge previously was one of three and one-half months' duration. In Martin and Smith's review one finds that the duration of the disease in fatal cases of systemic blastomycosis was less than six months in 20 (22%) of 91 cases.[7] The other patients lived from six months to three years or more. There was no statement made as to the case having the shortest duration. Bonoff reported, in 1950, 23 cases of acute primary pulmonary blastomycosis, in 6 of which there were positive roentgenographic findings.[8] These all, except for one case, occurred in army personnel in Okinawa in November and December, 1946. At least one of the patients died and showed the features of blastomycosis at autopsy. Bonoff states that the acute form of pulmonary blastomycosis appears to be characterized by: (*a*) a prodrome of three to four days and (*b*) localized chest pain. Organisms were found in the sputum and urine, and sometimes in both. Bonoff's article is not documented to show the organisms or lesions, but presumably there is no doubt of the diagnosis. Previous reports of such acute and nonfatal blastomycosis are not on record to my knowledge. This case indicates that brevity of clinical course does not exclude blastomycosis from clinical diagnostic consideration. It is impossible to draw any conclusion as to the effect of the antibiotics in influencing the course of the disease in this case either in a beneficial or a detrimental direction. "Stilbamadine" (4',4-stilbenedicarboxamidine) might have had a favorable effect in this acute case, as improvement from the use of this drug in chronic cases is said to be rapid.

SUMMARY AND CONCLUSIONS

Resection of mycotic lesions has proved effective in several fungus diseases. Resection of pulmonary lesions has been most successful in saprophytic fungus infection and in other mycoses in the following order: cryptococcosis, coccidioidomycosis, blastomycosis, and histoplasmosis. Histoplasmosis is last because it often is generalized or in both lungs, not because individual patients do poorly. Attention is called to mucormycosis and blastomycosis, which may be acutely fatal infections.

619 S. 19th St.

7. Martin, D. S., and Smith, D. T.: Blastomycosis (American Blastomycosis, Gilchrist's Disease): I. A Review of the Literature, Am. Rev. Tuberc. **39**: 275-304 (March) 1939; Blastomycosis (American Blastomycosis, Gilchrist's Disease): II. A Report of 13 New Cases, ibid. **39**: 488-515 (April) 1939.

8. Bonoff, C. P.: Acute Primary Pulmonary Blastomycosis, Radiology **54**: 157-164 (Feb.) 1950.

MANAGEMENT OF INTRACTABLE PAIN WITH ANALGESIC BLOCKS

John J. Bonica, M.D., Tacoma, Wash.

The management of intractable pain has been a difficult clinical problem that for centuries has taxed the diagnostic acumen and therapeutic skill of physicians. This has been due, in large measure, to the fact that until recently the fundamental nature of pain and pain mechanisms has not been well understood, and consequently the methods of diagnosis and therapy have in most instances been crude and empirical. During the past several decades the problem has captured the imagination of many brilliant laboratory and clinical investigators who have spent a great deal of effort and energy in unraveling the mysteries of pain. As a result of this coordinated scientific study, there is today a better understanding of the mechanisms of pain and consequently a more scientific approach to its management.

METHODS OF PAIN MANAGEMENT

The most rational therapy for pain should involve the interruption of the mechanism producing it. The first and best therapeutic method, therefore, is the abolition of the stimulus by removing the cause of pain. This can be done pharmacologically by administering such drugs as nitroglycerin and other spasmolytic agents for the relief of smooth muscle spasm, curare for relieving skeletal muscle spasm, and ergotamine for overcoming the vasodilation in migraine and other painful syndromes. These and other effects can sometimes be accomplished with physical or roentgen therapy or by injecting local analgesic agents. In some patients it may be necessary to extirpate surgically the lesion causing the pain.

Unfortunately, in some cases the cause of pain is unknown; or if it is known it cannot be eradicated, and other methods must be employed. The adjunctive methods presently employed in pain management are based upon the concept that the complex psychophysio-

From the Department of Anesthesiology, Tacoma General Hospital and Pierce County Hospital.

Read before the Section on Anesthesiology at the 101st Annual Session of the American Medical Association, Chicago, June 10, 1952.

logical phenomenon that is pain involves perception of noxious impulses and a reaction thereto. Some of these methods decrease or completely eliminate the perception; others are intended to modify the reaction to pain; still others affect both the perception and the reaction.

Clinically, the most commonly employed method involves the administration of narcotic analgesics and/or hypnotic drugs to reduce the perception of, and modify the reaction to, pain. The use of opiates and synthetic analgesics needs no further comment except to point out that frequently these drugs are misused. This is particularly true in managing intractable pain of undetermined origin, when there is a tendency for the busy physician to resort to the easier and less time-consuming method of administering analgesics. The undesirable side-effects on the respiratory, gastrointestinal, genitourinary, and central nervous systems, as well as the problem of addiction, must be considered when narcotics are employed for a prolonged period of time.

Neurosurgical operations to interrupt nervous pathways and thus prevent the perception of pain and the more recently adopted operations on the cerebrum to modify the reaction to pain are being used rather widely and successfully. However, these are destructive procedures. They are often mutilating and may result in serious complications and occasional failures.

Analgesic blocking, whereby local anesthetic agents are injected to chemically interrupt nervous pathways, is a very effective way of preventing the perception of pain. While the value of these procedures to eliminate pain inherent in surgical operations has been fully appreciated since Koller's discovery of cocaine in 1884, use of the nerve blocks in the management of nonoperative pain has lagged far behind. Although there were a few clinicians who had the foresight to employ the latter method early in the history of regional anesthesia, its use as a diagnostic and therapeutic tool in the management of intractable pain can be said to have gained recognition only in relatively recent years. The belated arrival of a procedure that had the promise of relieving pain without depressing bodily function or producing mutilating effects is not readily understandable. Certainly its use in the management of intractable pain is logical, since its primary role, the control of pain associated with chronically diseased or injured tissues, has a much broader application than surgical anesthesia.

Analgesic blocking in the management of intractable pain has certain advantages that may not be had with any other method. In properly selected patients this method is effective, and, when properly executed, it neither adds to the patient's discomfort nor is often followed by untoward reactions. It has the further advantages of not interfering with other forms of treatment and of usually requiring only minimal hospitalization. In some instances analgesic blocking not only relieves pain but also arrests the whole process of certain disturbed physiological mechanisms and brings about a return of normal function.

The indications for analgesic injections, or nerve blocking, fall within three main clinical categories: diagnosis, prognosis, and therapy. Diagnostic blocks can be used to determine the pathways of the pain and to aid in the differential diagnosis of diseases that present confusing signs and symptoms, such as coronary occlusion, pancreatitis, cholecystitis, ruptured peptic ulcer, renal colic, and appendicitis. Nerve blocks may be employed to differentiate trigeminal from glossopharyngeal neuralgia and other pain about the face and head. It may also be used to determine whether the patient has visceral or somatic pain, whether the pain is on a functional or organic basis, or whether the patient is malingering. Prognostic blocks are frequently performed to afford the patient the opportunity of temporarily experiencing the effects of interruption of a nerve before the interruption is made permanent. Moreover, analgesic blocking lends itself to the proper selection of patients for neurosurgical interruption and thus serves as an aid for the neurosurgeon to prognosticate the outcome of surgical operations in such conditions as tic douloureux, angina pectoris, causalgia and other reflex sympathetic dystrophies, neuralgia, pain associated with neoplastic diseases, and many other conditions. Therapeutic nerve blocks may be employed in the treatment of many painful syndromes. They may be used as a definite therapeutic measure in such self-limited diseases as thrombophlebitis, postoperative pain, herpes zoster and certain other neuralgias, visceral pain, and many other conditions accompanied by temporary, severe pain. Nerve blocks may be employed therapeutically to break up the vicious cycle of pain, such as occurs in reflex sympathetic dystrophies, in which pain relief may be complete or nearly so after one or several injections of the regional sympathetic ganglions. Analgesic injections also have a valuable place in providing symptomatic relief to permit other therapeutic measures, such as physical therapy and manipulation, or to allow time for more adequate preparation of the patient prior to surgical operations. In patients with severe intractable pain who are unsuited for surgery or who are unwilling to undergo the more major therapeutic offering, nerve blocks with phenol, alcohol, and other neurolytic agents effect relief for sufficient time to be of great value.

REQUISITES FOR OPTIMAL RESULTS WITH ANALGESIC BLOCKING

In recent years many physicians have been attracted to the performance of analgesic blocking for the management of pain and other nonsurgical diseases. The deceptive simplicity of injecting anesthetic solutions with a needle and syringe have led many to attempt these procedures without adequate knowledge of the various ramifications in this field, resulting in failures and at times accidents. The poor results and accidents have not been those intrinsic to this method but have been caused by the failure of the physician to learn something of pain and its nature and to realize the limitations inherent in this aspect of therapeutics. This has been particularly true of anesthesiologists who, having acquired certain skills and dexterity in executing nerve blocks for surgical anesthesia, are requested to perform these procedures for pain syndromes. It should be made clear at this point that I am not suggesting that these procedures are the sole responsibility of, or that they should be performed exclusively by, the anesthesiologist or any other specialist, for they can and should be employed by all interested practitioners. Rather, the purpose of this paper is to indicate that

the anesthesiologist or any other physician technically proficient with these procedures can play a significant role in the management of intractable pain, provided he complies with certain very important requisites.

Perhaps the first and one of the most important requisites is that the practitioner who performs analgesic injections for the management of pain, whether he be an anesthesiologist or not, must assume the responsibility and discharge the obligations of a physician rather than act merely as a technician who is an expert in inserting needles. It is essential that the physician give the patient with pain an intelligent appraisal so as to make a diagnosis of the over-all disease, and that he understand the underlying pain mechanisms and formulate a systematic plan for relief that will conserve the social usefulness of the patient. This is particularly important in the complicated problem of obscure pain of the intractable variety, in which the diagnosis and localization of its source require a thorough, detailed examination and a correct interpretation of medical, neurological, radiological, and laboratory data. There is more involved than merely the performance of a technical procedure. It becomes immediately apparent that proper management requires a great deal of time and effort, more than some practitioners are willing to spend, but unless the physician is willing to devote the necessary time to the problem he cannot hope to achieve optimal results. In fact, he may do more harm than good.

A proper diagnosis is an essential requisite for successful management of pain interruption. The anesthesiologist is frequently requested to perform a block for pain syndromes already diagnosed. In any case it is necessary to confirm or reject the diagnosis already made by the referring physician or other consultants, even though they may be reputable diagnosticians. Even if the diagnosis is obvious, it is advisable to investigate the problem fully, because in some cases additional information may be obtained that will aid in management. To this end a detailed history and thorough physical examination are important. In order to perform this properly, a thorough knowledge of pain syndromes and the underlying mechanism is required. In addition to making the diagnosis, taking of the history will afford the physician the opportunity to become acquainted with the patient, to investigate his personality, and, what is most important, to establish good rapport with him and win his confidence. This can be enhanced by bringing the patient a quiet, considerate humanity and a confidence and security based upon the conviction that all possible will be done to relieve him of his suffering. He must be made to feel that his unique individuality is recognized and that his problem is not meaningful to him alone.

After a diagnosis has been made, it is necessary to determine whether nerve blocking is indicated. It is important to employ analgesic blocks in indicated cases only; for, unless the haphazard and careless selection of patients is avoided, the results will be poor and the method will come into disrepute. If nerve blocks are indicated, it is necessary to decide what is to be accomplished with the procedure; that is, whether it is being performed for diagnostic, prognostic, or therapeutic purposes.

The patient should be fully informed about the various phases of the nerve block management. The purpose of the block, a general outline of the procedure, the effects that may be expected, what may be accomplished, and what is being sought must be clearly explained to the patient. If it is explained beforehand that the initial block may not produce the desired effects and that several blocks may be necessary before the efficacy of the method can be determined, the patient is less likely to become discouraged before all the treatment has been completed. The necessity for his cooperation should be particularly emphasized, for an informed patient is likely to be a cooperative patient. Throughout his discussion, the anesthesiologist must demonstrate full confidence in this method of management; for, unless the physician believes in the method himself, the results will be uniformly poor no matter how effectively the pain pathways are interrupted. This emphasizes the importance of recognizing the predominant psychological element of pain, particularly in the intractable variety. Although this is not the place for further elaboration of this point, it may still be stated that psychotherapeutic aids directed toward the modification of the reaction to pain are as important or more so than the prevention of the perception of pain. Unless the anesthesiologist or whoever performs nerve blocks for pain management realizes the importance of this facet of treatment and practices good clinical psychology along with the blocks, the problem will not be solved.

Another very important requisite is the ability to determine the pain pathway involved and the best technique of interrupting it. For this it is essential to have thorough anatomic and neurophysiological knowledge of pain pathways from all pain sensitive structures and the best point at which to interrupt them. The proper choice of blocking agents requires knowledge of their pharmacologic effects and experience in their use.

Some experience with the block procedure to be employed is another important requisite. Nerve blocks must be performed carefully and correctly, with meticulous attention to anatomic detail and with utmost gentleness. The practitioner should be fully acquainted with the structures that are traversed by the needle and the complications inherent in such procedures. It bears emphasis that haphazard introduction of a needle in the general area of a nerve in the hope that it will be anesthetized must be abandoned. Unpredictable variations in anatomy and tissue responses and the approach to nerves through the intact skin impose enough inaccuracy without introducing the additional one of improper execution due to a lack of knowledge of technique. This is particularly important when the block procedure is done for diagnostic or prognostic purposes, because in such instances much depends upon the results of the procedure. It is, therefore, essential to localize exactly and precisely the involved nerve or nerves. This can be accomplished by eliciting paresthesia, by checking the position of the needle by roentgen ray with or without prior injection of contrast media, and by employing small amounts of solution. Thus, while for therapeutic purposes in most instances a large amount of solution can be used without affecting the result of the block, such large amounts will

spill over and affect other nerves and are, therefore, contraindicated in diagnostic or prognostic procedures.

It is important to realize that the nerve-block method of managing intractable pain is not completely innocuous. Chemical neuritis and neuropathy with paralysis can occur; and, accidental pneumothorax, total spinal anesthesia, circulatory and respiratory collapse, and even death have been reported.[1] Unless the anesthesiologist is ready to admit that analgesic blocking has certain limitations, is replete with certain disadvantages, and is not infrequently attended by failure, the results will be disappointing to both patient and physician.

During and following analgesic block, it is essential to assess carefully the results as objectively as possible. Observation of the reaction of the patient to the formation of the intracutaneous wheal, to the insertion of the needle through pain sensitive structures, and to paresthesia aids in evaluating the problem. Following the block, the completeness of the interruption of the nerve impulses should be ascertained. When the adequacy of the block procedure is established, the desired effects for relieving the pain must be carefully assessed. This may require observation from a few hours to several days or weeks. The amount, type, and duration of relief obtained should be carefully noted and recorded.

TECHNIQUES OF ANALGESIC INJECTION

For obvious reasons, no attempt will be made to discuss techniques except to point out that any nerve capable of transmitting pain can be injected chemically to interrupt its conduction. Since experience can only be gained from performance, it is suggested that the physicians who assume the responsibility of executing these blocks for the management of nonsurgical pain become skillful and dexterous by first performing them repeatedly for surgical anesthesia. Unfortunately, since the introduction of thiopental (pentothal®) sodium, curare, and other deceptively innocuous agents, regional anesthesia for surgical operations is being done less and less and in general the art is being lost. I would like to make a plea for a reappraisal of the method and its more frequent employment in surgical anesthesia, for it not only offers surgical patients certain advantages but also enables physicians to gain proficiency in its use for the management of pain and other nonsurgical diseases. The subarachnoid injection of alcohol is a technique that merits special mention, because, when properly executed, it produces a chemical rhizotomy that compares favorably with surgical section; and it can therefore be used to afford relief from severe, intractable pain in patients who are unsuited for the more radical neurosurgical operations.[2]

Several adjuvant methods that are being presently employed to aid the execution of nerve blocks should be mentioned. The widespread use of roentgenograms to assist in the proper placement of needles, a procedure first suggested by Pollock and Potter[3] almost 40 years ago, has demonstrated the inaccuracy of many of the techniques used by even experienced physicians. The use of roentgenograms is particularly indicated in diagnostic and prognostic blocking and in some therapeutic blocks where small amounts of solutions are necessarily injected. More recently, preliminary injections of contrast media with subsequent roentgenographic visualization prior to injecting the analgesic solution have been employed in an effort to determine the diffusion of the injected solution.[4] Finally, the use of hyaluronidase to enhance the spread of local anesthetics and thus increase the success of nerve blocks has been acclaimed by some[5]; and while it should prove useful to the inexperienced regional anesthetist, it is not found necessary by the skilled operator. Because it probably accelerates the absorption of the local anesthetic, it may increase the incidence of toxic reaction.[5]

SOLUTIONS FOR ANALGESIC INJECTION

As previously mentioned, the proper choice of solution for injection is a most important consideration. For diagnostic and prognostic blocks that are intended to be completely reversible and of short duration, aqueous solutions of the commonly employed local anesthetic agents are the most satisfactory. Although procaine hydrochloride (in 1 or 2% solutions) for many years has been the standard drug, I have found 1 or 2% solutions of lidocaine (xylocaine®) hydrochloride and 0.1 or 0.2% solutions of tetracaine (pontocaine®) hydrochloride much more satisfactory — lidocaine for its short latent period and tetracaine for its longer lasting effects, which continue for as long as six to eight hours as compared with one to two hours for procaine.[6] Moreover, I have observed less toxic reaction following the use of tetracaine. Whenever a series of therapeutic blocks is indicated, tetracaine is used at intervals of one to five days.

For more prolonged blocking, various agents have been advocated. Oil solutions of local anesthetics, formerly recommended as a means of delaying the absorption of the analgesic agent and thus prolonging its action, have been found unsatisfactory because the blocks are frequently incomplete and unpredictable. Recently, a solution of procaine base and hydrochloride in polyethylene and propylene glycol, called "efocaine," was introduced for the purpose of producing analgesic blocks of several days' duration. The preliminary reports,[7] as well as my personal experience, are very encouraging and indicate that this drug holds great promise. In over 100 patients it effected a nerve block for an average of seven to nine days. Postinjection neuritis and pain were encountered in six cases. The use of ammonium compounds has been advocated by some authors,[8] who claim that such agents block only the unmyelinated fibers of somatic nerves, thus eliminating pain without interfering

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7. Iason, A. H., and Shaftel, H. E.: A New Approach to the Problem of Postoperative Pain, Am. J. Surg. **83**: 549, 1952.

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with other modalities of sensation. While a few patients have experienced prolonged relief from pain following the injection of such agents as "dolamin" (a solution containing benzyl alcohol, ammonium sulfate, and sodium chloride), most patients have not had such satisfactory results. The effects of these compounds cannot be predicted as to either completeness or duration. Since its use was first suggested by Mandl,[9] I have employed an aqueous solution of 6% phenol quite extensively to effect prolonged sympathetic interruption and have found this agent very efficacious. In some patients I have observed sympathetic interruption for as long as 13 months, although in most instances the block lasts from two to six weeks only. While the incidence, severity, and duration of neuritis after the injection of phenol is much less than that following the use of alcohol, complications do occur.

Benzyl alcohol in 0.75 to 2.0% concentration is a satisfactory agent for prolonged blocking; and although neuritis is occasionally seen subsequent to its use, it is mild and of short duration. Absolute alcohol remains one of the most effective drugs for prolonged interruption of nerve impulses. Unfortunately, its use is frequently followed by postinjection neuritis, but this usually is mild and lasts only a few weeks. Sometimes, however, it is so severe as to overshadow the original complaint. This complication is particularly serious in patients with psychosomatic disorders. Its use, therefore, should be reserved for the management of severe, intractable pain in patients unsuited for surgery or those who refuse operation. However, when properly administered in selected cases, it may produce relief of pain for many months, for years, or even permanently. Moreover, neurolytic injection of alcohol is certainly preferable to the drug addiction that so often follows management with narcotics or to the many serious complications that accompany some operations.

PAIN SYNDROMES MANAGEABLE WITH NERVE BLOCKS

The following brief discussion of painful conditions is included to indicate the use of nerve blocks in the management of intractable pain. It is based on my experience with this method during the past 10 years, during which period my associates and I administered over 5,400 analgesic injections to approximately 3,200 patients* for a great variety of conditions. A detailed analysis and account of these cases is in the process of being published.[10]

Neuralgia.—One of the common conditions amenable to nerve blocks is that of neuralgia, of which disease trigeminal neuralgia is the most distressing. Patients with this condition should receive one or two blocks with alcohol to afford relief and to give the patient the opportunity to experience numbness before retrogasserian neurectomy is done. In patients who are poor risks or those who refuse the operation, repeated alcohol blocks afford sufficient relief to be considered a good substitute for the operation. Tic douloureux involving the glossopharyngeal nerve is uncommon, but I have seen six cases in which the patients have been temporarily relieved with prognostic blocks and permanently cured with intracranial section of the nerve. Atypical neuralgias of the face may be managed with temporary cranial and/or cervical sympathetic blocks. The pain of occipital neuralgia is often permanently alleviated with temporary blocks of the occipital nerves or paravertebral blocks of the second and third cervical nerves. Sometimes an alcoholic injection is necessary to effect permanent relief.

Segmental neuralgia may be temporarily or even permanently relieved with paravertebral blocks using local anesthetics. The same may be said of herpes zoster pain. Postherpetic neuralgia, on the other hand, is a very difficult problem in that it is intractable to almost all treatment. In patients who are poor risks for rhizotomy, subarachnoid alcohol block affords relief with minimal complications. This procedure also holds true for neuralgia of leprosy and for severe, intractable "idiopathic" intercostal neuralgia. Of course, a thorough preliminary examination should be made where the latter condition exists in order to exclude the possibility of spinal cord tumors, herniated disks, and other organic lesions that can be eliminated surgically. Radiculitis may indicate a diagnostic-prognostic block to determine the segments involved and the effect rhizotomy will have on the pain. In poor risk patients, alcohol injected in the subarachnoid area may be employed to afford prolonged relief of pain, as it can also be used in cases of lumbar and lumbosacral neuralgia. Meralgia paraesthetica is a neurological condition that involves the lateral femoral cutaneous nerve and may be due to a variety of causes. If elimination of the cause is impossible, a prognostic block may be done to determine the probable effect of surgery, or a prolonged block may be established for semipermanent relief.

Causalgia and Other Reflex Sympathetic Dystrophies.—Major causalgia is a condition that is due to incomplete severance of a major peripheral nerve, such as the median or sciatic, and is characterized by severe burning pain, hyperalgesia, and vasomotor and sudomotor disturbances. This condition is very seldom seen in civilian practice, but it is one of the most difficult problems that confront the military surgeon during wartime. During the second World War, I saw nine such cases that were treated with sympathetic nerve blocks. Temporary relief was afforded in eight patients, although only three obtained permanent relief of pain with this method. This is in contrast to the four recently treated casualties in whom I effected prolonged and, I hope, permanent relief of pain. The difference in the outcome may have been due to the fact that the patients in the first group were not treated until several months after injury, whereas those of the second group were seen within weeks after their injuries. This illustrates the importance of early treatment in these cases.

Minor causalgias, post-traumatic pain syndromes, and post-traumatic osteoporosis are frequent and serious problems that confront all physicians but particularly those who practice industrial medicine. These conditions are very important, because they present confusing symptoms and often remain undiadgnosed for a long

* These include a large number of patients treated in Madigan Army Hospital, Tacoma.

9. Mandl, F.: The Paravertebral Block in Diagnosis, Prognosis, and Therapy: Minor Sympathetic Surgery, New York, Grune & Stratton, 1947; Aqueous Solution of Phenol as a Substitute for Alcohol in Sympathetic Block, J. Internat. Coll. Surgeons **13**: 566, 1950.

10. Bonica, J. J.: The Management of Pain, Philadelphia, Lea & Febiger, to be published.

period of time. The same may be said of the shoulder-hand syndrome and other reflex sympathetic dystrophies. It is generally agreed that, like major causalgias, these conditions just mentioned involve the sympathetic nervous system, and blocking the sympathetic ganglions that supply the affected part will temporarily improve the condition. In some cases a series of blocks will effect permanent relief, particularly if these are done early.

Phantom limb pain is another form of reflex sympathetic dystrophy that may respond to nerve blocking, if done early. Three patients who were treated with nerve blocks within a few weeks after the phantom limb became painful experienced complete relief of pain, which has not recurred for a period of five, three, and two years respectively. On the other hand, I have seen several other patients who had had intractable pain for several years and who did not respond to any form of therapy. Prognostic total spinal block did not relieve their pain, even though anesthesia extended to the cervical dermatomes. This again illustrates the importance of early treatment, for unless these patients are treated early they become chronically affected and are very difficult to manage. Furthermore, a "central pain pattern" often develops, relief for which can be effected only by radical neurosurgical procedures in the frontal lobes.

Pain Consequent to Vascular Disease.—The pain that is present in such peripheral vascular diseases as thrombophlebitis, Raynaud's disease and other vasospastic conditions, thromboangiitis obliterans, and arteriosclerosis can be temporarily relieved with sympathetic nerve blocks. The pain and edema of thrombophlebitis due to the existing reflex vasospasm can be ameliorated with repeated sympathetic blocks. This procedure greatly diminishes the morbidity and affords relief, which is appreciated by the patient, and in addition it will prevent the occurrence of postphlebitic edema. The same gratifying results can be obtained in frostbite and acute arterial catastrophies. My associates and I have used sympathetic blocks to treat a large group of patients with frostbite sustained in Korea and have observed excellent results. In most instances of Raynaud's disease, thromboangiitis obliterans, and arteriosclerosis, blocks are used solely to prognosticate the effects of sympathectomy. In some poor risk patients, however, prolonged blocks often afford prolonged relief. Diagnostic blocks with local anesthetics or therapeutic nerve blocks with alcohol are useful for the pain of aortic aneurysm.

Visceral Pain.—Diagnostic and therapeutic nerve blocks may be valuable for patients with visceral pain. The pain of pulmonary embolism can be dramatically relieved with stellate ganglion blocks. Discomfort due to asthma may also be alleviated with the same procedure. The pain of pleurisy can be relieved with intercostal nerve blocks. The severe, excruciating, and intractable pain of acute pancreatitis can be relieved by blocking the celiac plexus or the 6th to 10th thoracic sympathetic ganglions. These procedures, in addition to the relief of pain, improve the patient's condition by releasing the visceral vasospasm. The severe pain of gallbladder colic, peptic ulcer, and renal colic can be temporarily relieved by blocking the appropriate sympathetic ganglions. The same may be said of other types of visceral pain, including cardiospasm, dysmenorrhea, and cystitis.

Musculoskeletal Pain.—The pain of such conditions as ankle and other joint sprains, fractured ribs, fractured vertebrae, painful hip, acute torticollis, low back pain, painful shoulder, bursitis, tendinitis, periarthritis, and acute myalgias can be permanently relieved by repeated blocks using solutions of local anesthetics. This method of therapy affords sufficient pain relief to allow active mobilization and the use of physiotherapeutic measures and thus enhance a rapid improvement. In order to obviate the disadvantages of opiates in postoperative pain, intercostal blocks may be done with solutions of longer acting agents such as tetracaine hydrochloride or dibucaine (nupercaine®) hydrochloride, or with "efocaine," and may thereby prevent postoperative pulmonary complications.

Pain of Malignant Growth.—The excruciating pain that is often present in malignant diseases may be adequately relieved with alcohol nerve blocks. While this method has certain limitations and cannot be considered as the only form of definitive therapy for these painful states, it does offer certain advantages that may not be had with other forms of treatment. Properly executed nerve blocks can effect complete relief of pain and enable the sufferer to tolerate more intensive x-ray and radium therapy and other forms of medical treatment that would not ordinarily be tolerated. In addition, blocks are not accompanied by the severe central nervous system depression that is inherent in massive opiate therapy, nor do they impose the risk of major surgical procedures that are usually not tolerated by poor risk patients. Most clinicians who have had much experience in coping with this problem are of the opinion that in the majority of poor risk patients with intractable pain from an inoperable malignant condition, alcohol nerve blocking is the method of choice. In a group of 137 patients with severe, intractable pain associated with neoplastic diseases treated with prolonged nerve blocks, 64% obtained complete relief until they died, 23% obtained moderate relief, and 13% obtained only minimal or no relief.[11]

SUMMARY

Attention is again called to the fact that the management of intractable pain is a difficult clinical problem that should interest every practitioner and that frequently requires the joint effort of several physicians in various fields. The anesthesiologist or any other physician who is proficient in executing analgesic blocks can play a significant role in the management of patients with intractable pain, provided he observes certain requisites. A correct diagnosis, an understanding of pain mechanisms, an adequate knowledge of the anatomy and neurophysiology of pain, a thorough knowledge of the techniques and the agents best suited for various analgesic blocks, and an objective assessment of the results are important requisites without which optimal results cannot be realized. Mention is made of various pain syndromes to indicate the value of analgesic blocks in their management.

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CORTISONE THERAPY IN ULCERATIVE COLITIS

G. Malcolm Brown, M.D.
and
John S. McAuley, M.D., Kingston, Ontario, Canada

Reports are now available on the results of cortisone therapy in small groups of patients with ulcerative colitis. Dearing and Brown [1] treated four patients with small dosages and induced a remission in one. Kirsner, Palmer, and Klotz [2] treated five patients with chronic ulcerative colitis and found definite though gradual improvement in two, rapid improvement in one but with early and refractory remission, no response in one, and in another a poorer response than was subsequently seen with corticotropin (ACTH). Halsted and associates [3] treated four patients with cortisone dosages up to 250 mg. per day to a total of 2,600 mg. and had excellent results in one and slight improvement in two. Redish [4] saw no improvement in two patients with chronic cases in acute exacerbation treated with dosages of 100 to 200 mg. over 10 day periods but did see slight improvement in two of three patients with chronic cases treated with the same order of dosage. Machella and Hollan [5] found no improvement in two of three patients receiving a cortisone dosage of 1,500 mg. over 10 days. Gray and his colleagues [6] have treated four patients with severe and intractable ulcerative colitis. Others have treated one or two patients.[7] In all these cases the cortisone dosages used have often been rather small. Where there has been opportunity for comparison of the effect of corticotropin and cortisone, the impression has been that corticotropin has a more rapid and dependable action than cortisone in the dosages used.[8] Kirsner, Palmer, and Klotz [2] found in their series that the changes in eosinophils, urinary and fecal nitrogen, and uropepsin were less pronounced and more erratic with cortisone than they were with corticotropin.

Cortisone has now been used in a larger series of patients with results that show a great difference in response in the acute case or the chronic case in an acute exacerbation as compared with the chronic, unremitting type of case. This points to the need for detailed case information if comparisons are to be made between one series and another. The results also show the need for a higher and more prolonged dosage schedule than has been used in many of the previous trials.

MATERIAL AND METHOD OF TREATMENT AND STUDY

Eleven courses of cortisone therapy were given to nine patients, admitted consecutively, 9 to 42 years of age, with an average illness duration of four to nine years. The diagnosis of ulcerative colitis was established in each case and confirmed by radiographic study and sigmoidoscopic examination, with numerous stool examinations to exclude specific pathogens. Three patients were considered examples of acute ulcerative colitis with comparatively short periods of illness of from 8 to 14 months, with severe diarrhea, pyrexia, variable toxemia, and much loss in weight. There were six patients with chronic ulcerative colitis with established symptoms ranging over 2½ to 12 years. Four of these patients had a severe relapse over the period of two to six months prior to cortisone treatment and were definitely manifesting an acute phase of their chronic illness. The other two patients exemplified the continuous, unremitting type of chronic ulcerative colitis. They had carried on for 8 and 12 years respectively with moderate incapacity but no prominent episodic exacerbation, and both enjoyed a reasonably good nutritional status.

In addition to regular clinical observations and the usual graphic charting, the case study included a daily record of the patient's weight and the frequency and character of the bowel movements. Serial determinations were made of the red and white blood cell counts, hemoglobin level, sedimentation rate, and plasma protein level. Roentgen studies and sigmoidoscopy were made at the beginning and end of the treatment period and also when indicated by clinical change. Follow-up examinations were scheduled in cases where the patient was discharged from the hospital.

The criteria of response to therapy were confined to specific objective features of the local and systemic manifestations of the disease. The indexes of systemic improvement included the temperature, the weight, the hemoglobin level, the sedimentation rate, and the fractionated plasma protein level. These specific data are generally reliable indications of general bodily status, and their serial change was stressed in this study. The therapeutic response in terms of local changes was as-

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From the Department of Medicine, Faculty of Medicine, Queen's University.

A part of the cortisone used in this study was provided by the National Research Council.

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8. Kirsner,[2] Halsted,[3] Gray,[6b] Kirsner, J. B., and Palmer, W. L.: Effect of Corticotropin (ACTH) in Chronic Ulcerative Colitis: Observations in 40 Patients, J. A. M. A. **147:** 541 (Oct. 6) 1951.

sessed with progressive x-ray studies, by direct visualization of the mucosa, and in the trend of the diarrhea as manifested by stool character and frequency. There is a considerable lack of parallelism in these different changes, and in the final analysis all the factors involved were given equal emphasis in the ultimate assessment in each case.

Cortisone was used in total amounts ranging from 2,300 to 8,500 mg. for periods varying from 13 to 115 days. The average treatment schedule was 44 days. In most cases the initial dosage of cortisone was 100 mg. three times a day, and the symptomatic response governed decrease (or increase) in this level. Throughout the schedule, reduction in dosage was generally made with regard for the maintenance of an optimal clinical response. Cortisone was withdrawn carefully at the end, in most cases gradually over a period of 10 to 21 days. In three patients orally administered cortisone predominated in treatment, while three patients received all the hormone by the intramuscular route. The other three patients were given the greater part of the total amount of cortisone by intramuscular injection. It was our impression that the effect of cortisone in acutely ill patients was more assured and possibly more rapid when given by the intramuscular route. General management consisted of the usual dietary measures and other supportive treatment. Sodium chloride restriction and potassium chloride by mouth were used in six patients.

Summary of Results in Nine Patients During Cortisone Treatment for Ulcerative Colitis

	Acute Colitis						Chronic Colitis—Acute Relapse								Chronic, Unremitting Colitis			
Patient	1		2		3		4		5		6		7		8		9	
Cortisone dosage	4,500		7,800		4,000		8,350		8,500		5,150		2,300		3,600		2,700	
Days of treatment	57		55		42		115		42		34		13		25		17	
Before and after treatment	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
Hemoglobin level, gm./100 cc.	12.0	13.7	13.7	13.3	11.0	13.3	12.1	12.8	8.9	9.8	9.6	8.0	11.0	11.4	12.8	12.7	11.7	11.6
Sedimentation rate, mm./hr.	37	17	18	15	66	27	45	10	95	84	107	118	37	28	2	4	45	30
Total plasma protein level, gm./100 cc.	7.1	6.8	5.5	....	4.9	7.2	6.1	5.4	3.8	5.4	...	...	5.8	6.4	6.3	6.3	7.8	7.5
Albumin, gm./100 cc.	4.2	4.4	3.6	....	2.4	4.4	3.3	3.5	2.7	3.4	...	...	2.9	3.7	4.4	4.1	4.6	4.4
Globulin, gm./100 cc.	2.9	2.4	2.0	....	2.5	2.8	2.8	1.9	1.1	2.0	...	...	2.9	2.7	1.9	2.2	3.2	3.1
Stools, avg. no./day	5	1	18	6	7	1	13	2	15	4	20	6	9	2	7	7	4	4
Weight, lb.	88	102	68	84	125	157	90	108	106	115	85	97	156	61	127	127	135	134
Change in rectal mucosa	Return to normal		Marked improvement		Marked improvement		Considerable improvement		Almost normal in 3 months		Marked improvement		Slight improvement		No change		No change	
Radiographic change	Little change		Worse		Slight improvement		Worse		Worse		Worse		No change		No change		No change	
Over-all result	Rapid improvement		Gradual improvement		Rapid improvement		Marked improvement		Slow response, later remission		Moderate improvement		Rapid improvement		No response		No response	

RESULTS

Systemic and General Response.—The general trend of results (see table) indicated the good effect of the hormone in the acute phase of ulcerative colitis. The three patients with acute colitis in this series responded favorably as did the four patients with chronic cases in acute relapse, but there was no remarkable improvement in the two patients with unremitting cases of chronic ulcerative colitis. Favorable improvement was manifested by decreased diarrhea, gain in weight, lowered sedimentation rate, usually an increase in hemoglobin concentration, and an improvement in the mucosal changes as seen on sigmoidoscopy. In two patients a dramatic remission was rapidly induced, and a third patient obtained complete remission of symptoms very early in treatment. Of these patients, one has continued in remission 19 months to date of this writing, one relapsed after 3 months, and the third patient, after six weeks of remission, underwent surgery because of a stricture in the sigmoid colon. There was remarkable alleviation of the manifestations of the disease in four patients, two of whom progressed to complete symptomatic remission shortly after cessation of cortisone, and one has still maintained this status at nine months. The remarkably improved condition of one patient continued six months, after which a further degree of improvement occurred. Another patient suffered a relapse when cortisone was withdrawn, and later he had a colectomy.

A favorable systemic response was usually heralded by prompt subsidence of the fever, followed in a few days by the disappearance of clinical signs of toxemia. A gain in weight was later manifested and in the long run was not a reflection of edema, as minor sodium chloride and water retention were dealt with adequately. The average increase in weight in seven patients responding favorably to cortisone therapy was 15 lb. (6.8 kg.), whereas no significant weight gain occurred in the two patients with chronic, unremitting ulcerative colitis. Serial estimations of the red blood cell count and hemoglobin level indicated improvement, particularly in those patients with fairly pronounced secondary anemia prior to treatment. The sedimentation rate improved in five patients, returning to normal range in three. A minor fluctuation of doubtful significance was seen in the others. The total plasma protein levels increased remarkably in two patients who began treatment with very low levels; a slight decrease occurred in two others. In three patients there was a slight increase in albumin and a decrease in globulin.

Local Response.—Control of the diarrhea was the outstanding indication of local improvement. There was a dramatic reduction in the number of stools in the patients who quickly went into remission, but the gradual

decrease in stool frequency in other patients did not indicate a less gratifying final result. In most cases the fairly rapid disappearance of blood from the stools was an early feature of the response, and the distressing urgency of defecation subsided with the onset of semiformed stools. Two patients in the series showed a dramatic response on the fourth day of treatment when each began to have one daily formed stool. The other patients varied in rapidity of the control of diarrhea. In one case the onset of general symptomatic remission in the second week was preceded by decrease in stools to one or two a day. In another case the daily occurrence of 15 to 20 stools subsided to two semiformed movements after three weeks of cortisone therapy. One patient with three or four stools each night was relieved in the second week when the stools became semiformed and the nocturnal diarrhea disappeared. In two patients, whose general response was favorable, the control of diarrhea was slow and only occurred gradually over the entire treatment period, but improvement continued after treatment and in both cases there was remission. There was no reduction in stool frequency in the two patients with long-standing, unremitting symptoms.

The mucosal changes occurred more gradually and were not grossly apparent on sigmoidoscopy during the initial two or three weeks of improvement. The degree of mucous membrane improvement roughly followed the earlier pattern of symptomatic response, and in the nine patients studied the change varied from slight to marked in the acute or in the acute on chronic cases, with no apparent mucosal change in the two patients with unremitting cases of ulcerative colitis. In one patient there was a return to normal appearance of mucosa within one month of treatment; in another, at the end of three months, there was only a little purpura on the posterior rectal wall. Pronounced mucosal improvement in three patients was manifested by very much less ulceration and bleeding and in one by definite regression in pseudopolyp formation. Less extensive ulceration and hemorrhage noted at the end of treatment in two other patients were judged comparatively as slight and as moderate improvement. Stricture formation in one patient with the unremitting symptoms was unchanged.

The radiographic changes were not striking, and during the periods of greatest clinical improvement there was no change. At the end of treatment in two patients, there was an apparent increase in the caliber of the colon, probably reflecting less spasm; in another the bowel appeared narrower and more spastic than before treatment. In three patients there was more extensive involvement of the colon radiologically, despite mucosal and general clinical improvement. In three patients there was no change in the frequency of bowel movements at the end of treatment.

REPORT OF CASES

CASE 1 (patient 3 in table).—Acute ulcerative colitis (fig. 1): A 23-year-old man with a 14 month history of ulcerative colitis had suffered a severe diarrhea of 8 to 10 watery movements daily for over 3 months and had lost 35 lb. (15.9 kg.) in weight. He was very toxic and febrile, with temperatures ranging between 100 and 103 F (37.8 and 39.4 C). Sigmoidoscopy revealed congestion, friability, and very marked polypoid change. Radiological examination showed involvement of the entire colon and a portion of the terminal ileum, with evidence of marked polypoid change. Laboratory investigations revealed: red blood cell count 3,800,000, hemoglobin level 11 gm. per 100 cc., white blood cell count 15,000, sedimentation rate 66 mm. per hour, total plasma protein level 4.9 gm. per 100 cc., albumin 2.4 gm. per 100 cc., and globulin 2.5 gm. per 100 cc.

Cortisone therapy was started (by intramuscular injection for the first 4 days) with 200 mg. the first day, 200 mg. daily for 5 days, 100 mg. a day for 18 days, and then a reduction to 50 mg. daily for another 18 days. A total dosage of 4,000 mg. was given over 42 days. There was a rapid subsidence of fever and toxemia, and the stools were formed after the fourth day and were of normal frequency. By the end of the first week the patient had a ravenous appetite and his spirits were high. This dramatic remission continued, and the patient gained 32 lb. (14.5 kg.) and looked very much better. Serial laboratory determinations reflected an increase in hemoglobin concentration and a rise in plasma protein levels as well as a major decrease in the sedimentation rate to near normal range. The mucous membrane at the end of treatment was still erythematous and slightly friable, but the rectum showed much less polypoid change. Radiographically the gut was of normal diameter, but haustral markings were still absent and there was marked polypoid change.

The symptomatic remission in this case lasted three months, and the relapse, which occurred seven weeks after cessation of cortisone therapy, was featured by the return of diarrhea without blood or pus and with no fever or weight loss. A second course

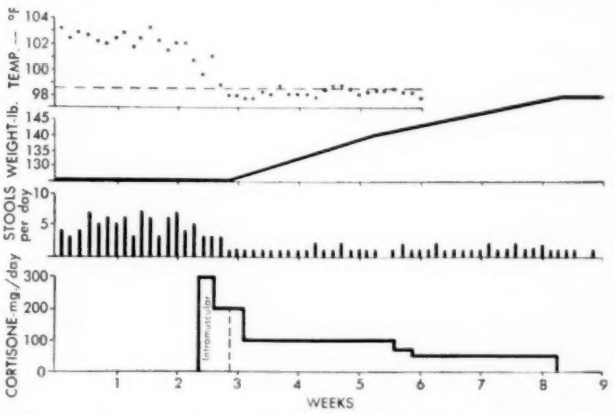

Fig. 1 (case 1).—Results obtained through the use of cortisone therapy in a patient with acute ulcerative colitis.

of cortisone, 1,125 mg. over 11 days, obtained prompt and good results; but two and one-half months later the patient relapsed again and received a third schedule of cortisone, 2,700 mg. over three weeks. There was a moderately good effect. He gained 7 lb. (3.2 kg.), and the diarrhea subsided; but within a few weeks perirectal suppuration and fistulas with symptomatic exacerbation developed and he later underwent a total colectomy.

CASE 2 (patient 5 in table).—Acute on chronic ulcerative colitis (fig. 2): Chronic ulcerative colitis of low-grade severity was present in a 31-year-old woman, who had carried on a nearly normal existence over a period of six years with only moderate degree of incapacity. She suffered an acute exacerbation of her illness following an upper respiratory infection and within two months lost 20 lb. (9.1 kg.) in weight, with a severe diarrhea of 15 to 25 bowel movements daily containing gross blood and mucus. She became extremely toxic and febrile, with a temperature ranging from 101 to 104 F (38.4 to 40.0 C). Generalized abdominal tenderness was pronounced, and on several occasions there were signs of localized peritoneal irritation. Sigmoidoscopic examination revealed the greater part of the rectal mucosa to be ulcerated and bleeding freely, and radiological examination showed loss of haustral markings in the sigmoid and lower half of the descending colon. The laboratory investigations were as follows: red blood cell count 3,120,000, hemoglobin level 8.9 gm. per 100 cc., white blood cell count 11,350, sedimentation rate 95 mm. per hour, total plasma protein level 3.8 gm. per 100 cc., albumin 2.7 gm. per 100 cc., and globulin 1.1 gm. per 100 cc. (albumin-globulin ratio 2.4).

Cortisone was given orally, 300 mg. daily in divided doses during the first two weeks, with an additional 100 mg. on the seventh and eighth days; and for the next nine days the patient received 225 mg. per day, followed by four days at the 200 mg. level, then six days of 150 mg. a day. The dosage was then tapered gradually over a 10 day period, ending on the 42nd day of treatment (8,500 mg. total dose).

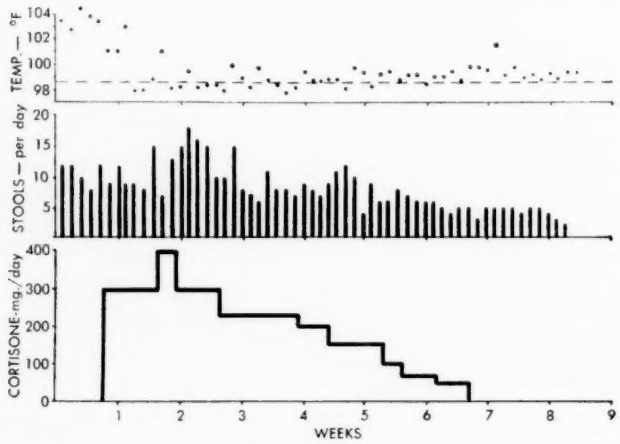

Fig. 2 (case 2).—Results obtained through the use of cortisone therapy in a patient with chronic ulcerative colitis in acute exacerbation.

In this case the temperature dropped to normal on the fourth day, but the response in terms of reduction of stools was slow and only occurred gradually over the entire six weeks of treatment. The stools were free of blood and mucus and numbered three to five per day at the end of treatment; one week later they were further reduced to two or three per day. The hemoglobin level was 9.3 gm. per 100 cc., and the sedimentation rate showed a minor drop to 84 mm. per hour. The total plasma protein level had increased to 5.4 gm. per 100 cc., the albumin fraction to 3.4 gm. per 100 cc., and the globulin level was 2.0 gm. per 100 cc., with the albumin-globulin ratio at 1.7. The rectal mucosa appeared rough and granular and bled freely on trauma. Radiological examination demonstrated involvement of the entire colon; there were narrowing of the lumen and a moth-eaten appearance throughout the entire length.

The general response in this case was slow, but during treatment the signs of toxemia quickly disappeared, and there was great objective improvement in the rectal mucosa at the end of cortisone therapy. The patient went on to a complete symptomatic remission but not faster than in cases of spontaneous remission. If this patient were being treated over again, the hormone would be given intramuscularly during the initial period, but at the time of actual therapy the cortisone was given by mouth to determine the effect in such cases. The remission in this patient has been maintained to the date of writing (nine months after leaving the hospital), and she is now working. She has one to three formed stools a day without blood or mucus, and the rectal mucosa shows only a little purpura on its posterior wall.

Case 3 (patient 8 in table).—Chronic, unremitting ulcerative colitis (fig. 3): A 37-year-old woman had carried on her professional work for 12 years despite the unremitting diarrhea of a moderately severe ulcerative colitis. Her general nutritional status was reasonably good, and she had recently gone through a pregnancy without mishap. Sigmoidoscopy showed a roughened granular mucosa, with a few small ulcers and a stricture in the upper rectum. Radiographically the entire colon was observed to be shortened and narrowed. Laboratory investigation revealed: red blood cell count 4,200,000, hemoglobin level 12.8 gm. per 100 cc., white blood cell counnt 5,350, sedimentation rate 2 mm. per hour, total plasma protein level 6.3 gm. per 100 cc., albumin 4.4 gm. per 100 cc., and globulin 1.9 gm. per 100 cc.

Cortisone was given intramuscularly, 300 mg. the first day, 200 mg. daily thereafter for 1¼ days, and then a reduction to 100 mg. a day, with a total dosage of 3,600 mg. administered over 25 days. In this case there were no general systemic response and no change in the diarrhea, and laboratory examinations showed little serial change. Studies of stool volume and nitrogen content during the first two weeks of treatment showed no significant change. On sigmoidoscopy the mucous membrane appearance and the rectal stricture were not altered at the end of treatment. Hormone treatment had little apparent effect in this unremitting case of ulcerative colitis, but it is to be noted that in this case, as well as in the other case of chronic, unremitting ulcerative colitis, the amount of hormone used was relatively small and the course of treatment relatively short.

COMMENTS

The changes seen when a remission is induced by cortisone therapy in a patient with ulcerative colitis are similar to those seen in a spontaneous remission, and the order in which they occur is also the same. There is first of all a decrease in the diarrhea and a fall in temperature to normal levels, with subsidence of the toxemia. Changes in the mucous membrane follow, and it may be a considerable time before it returns to normal. Except perhaps for a disappearance of spasm, the radiographic changes, the resolution of the pseudopolyps, the opening up of the strictures, and the return of haustration occur only over a period of many weeks or months of continued remission. A patient in a cortisone induced remission is in the same position of potential danger as the patient who has had a spontaneous remission. There is the same delay between symptomatic remission and the repair of damage to the fibrous and muscular tissue of the bowel wall, and there is the same danger of relapse. For these reasons these patients must have the same care and attention that they had before cortisone therapy, and the use of cortisone should not mean the abandonment of any of the other established therapeutic measures during either the acute phase or the remission period.

Cortisone may have an important role as an adjunct to psychotherapy in ulcerative colitis. In the past, psychotherapy in this condition has been difficult because of the resistance often shown to more than superficial exploration and because unwise psychotherapy often led to a worsening of the colitis and in some cases to the development of a frank psychosis. McKell, Tuthill, and Sullivan [7b] have commented on the increased accessibility

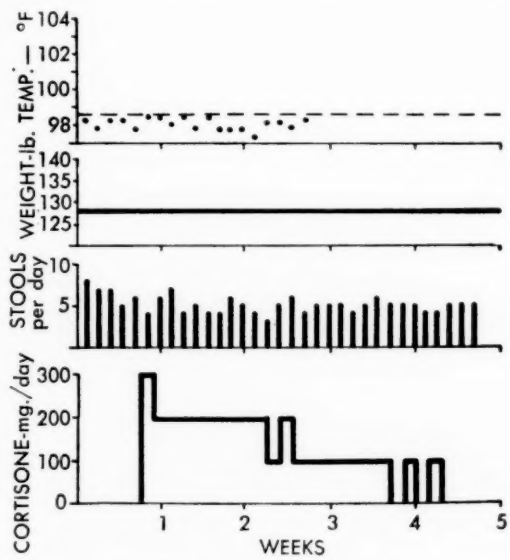

Fig. 3 (case 3).—Results obtained through the use of cortisone therapy in a patient with chronic, unremitting ulcerative colitis.

of a colitis patient after cortisone therapy was instituted. Hormone therapy should also protect against deterioration of the bowel condition itself.

The experiences that have been reported now indicate the need in some cases for very large doses at the beginning of treatment for ulcerative colitis. Enough should be given to control the fever, toxemia, and diarrhea; and in acute cases with very severe diarrhea, cortisone is better given by the intramuscular route. When this is done, improvement may be just as rapid as with corticotropin. Our experience also shows the necessity for prolonged treatment, and it is our opinion that the daily dose should be sufficient to maintain symptomatic improvement until there have been very definite changes for the better in the mucous membrane. This means in the majority of cases a much larger dosage than has been used in earlier series, and our results show that when these larger and more prolonged dosages are used the results are better than those previously reported. When the dosage is large there may be water retention, but in our series this was easily dealt with by sodium chloride restriction. Whenever this alone is ineffective, it is probably preferable to use a mercurial diuretic rather than to give ammonium chloride. If treatment is preceded by prolonged and severe diarrhea, potassium deficiency may arise when the potassium loss of cortisone therapy is added to that of the diarrhea, and this should be guarded against by serum potassium determinations.

SUMMARY

Eleven courses of cortisone therapy have been given to nine patients with ulcerative colitis. In three acute cases and in four chronic cases in acute exacerbation, the results were good. In two examples of the chronic, unremitting type of the disease, no response was seen in the dosages used. If treatment is to be successful, the dosage of cortisone should be larger and more prolonged than has often hitherto been used in this disease. The remission induced by cortisone is similar to the spontaneous remission, and there is the same danger of relapse.

PRELIMINARY CLINICAL EVALUATION OF THROMBIN RECOVERY TEST

L. A. Sternberger, M.D., Albany, N. Y.

The laboratory diagnosis of thrombosis has been difficult because of the absence in circulating blood of the two essential products of coagulation, thrombin and fibrin. The fibrin is fixed at a local site, while the excess of thrombin formed becomes inactivated immediately by antithrombic substances. Recently a method for recovering such inactivated thrombin has been developed,[1] and elevated values have been demonstrated in thrombosis produced experimentally in rabbits. The method has now been applied to patients, and the present paper reports on these clinical observations.

METHODS

The recovery of thrombin is accomplished by dissociating the thrombin-antithrombin complex with alkali slightly above freezing temperature and by preventing its reassociation upon neutralization through the addition of ethyl alcohol to a final concentration of 25%. Nine milliliters of venous blood are obtained with siliconized syringes [2] containing 1.0 ml. of 4% sodium citrate solution. Siliconized needles (19 gauge) are used. The plasma obtained by centrifugation is stored at about 5 C and tested as early as feasible.

Satisfactory conditions for dissociation can be obtained by the use of a 50 ml. beaker placed in a 400 ml. beaker. The 400 ml. beaker is filled with water to about a third of the height of the 50 ml. beaker, which is kept in position by a suitable weight (for instance, two no. 8 rubber stoppers). The 50 ml. beaker is then frozen in place inside the 400 ml. beaker in a freezer at from –10 to –20 C. Immediately before carrying out the dissociation, such a beaker pair is removed from the freezer and 2.5 ml. of 0.85% sodium chloride solution, which has been stored in a refrigerator at 2 to 8 C, and 2.5 ml. of plasma are placed in the 50 ml. beaker. The mixture is made alkaline, employing a Beckman, model G, pH meter with calomel and general purpose glass extension electrodes (for use to –5 C). The electrodes are standardized at room temperature with pH 10.0 buffer (Beckman standard buffer), and the temperature compensator of the pH meter and the instrument controls are then adjusted to 2 C. Magnetic stirring is employed for mixing the sample. A plastic covered magnet 3/8 inch long is put into the 50 ml. beaker containing the plasma and the saline, the beaker pair is placed on the magnetic stirrer in such a way that the magnet spins in an eccentric position in the 50 ml. beaker, and the extension electrodes are inserted into the opposite side of the beaker. While pH adjustments are carried out, the magnetic stirring is occasionally aided by slight manual agitation of the containers.

Five to six drops of 0.5 normal sodium hydroxide solution in 25% ethyl alcohol [3] are added, followed by a sufficient quantity of 0.05 normal sodium hydroxide solution in 25% ethyl alcohol [3] to balance the pH meter at pH 11.3.[4] The reagents are held at this pH and temperature for two minutes, and 5.0 ml. of 50% ethyl alcohol [5] stored at from –10 to –20 C are added. The

From the Division of Laboratories and Research, New York State Department of Health.

Dr. John H. Mulholland, Director of the Third Surgical (New York University) Division, Bellevue Hospital, facilitated the study of patients in his department and gave much guidance in this work. Dr. William S. Tillett, Director of the Third Medical (New York University) Division, Bellevue Hospital, permitted the study of medical cases, and Dr. William T. Helmuth, Assistant Director in charge of the Branch Laboratory of this division, also helped in this work.

1. Sternberger, L. A., and Maltaner, F.: The Recovery of Preformed Thrombin from Circulating Plasma, Science **114**: 414-416 (Oct. 19) 1951.

2. Jaques, L. B.; Fidlar, E.; Feldsted, E. T., and Macdonald, A. G.: Silicones and Blood Coagulation, Canad. M. A. J. **55**: 26-31 (July) 1946.

3. Twenty-five per cent alcohol was made up with 50% ethyl alcohol in 0.85% sodium chloride solution.

4. This pH corresponds to pH 11.2 if a high pH glass electrode is used and the low temperature correction is calculated instead of employing the automatic temperature compensator at 2 C (which is beyond the range for which its use is intended).

5. Fifty per cent alcohol was prepared by making up 52 volumes of 96% ethyl alcohol to 100 volumes with 0.85% sodium chloride solution.

mixture is neutralized by adding 5 to 6 drops of a 0.5 normal solution of hydrochloric acid in 25% ethyl alcohol [3] followed by a sufficient quantity of 0.05 normal hydrochloric acid in 25% ethyl alcohol [3] to balance the pH meter at pH 7.2.

The suspension of recovered thrombin, after its volume is measured to the nearest milliliter, is brought to 18 C with occasional shaking (using a water bath cooled by tap water running through a coil). The clotting activity of the recovered thrombin suspension is determined in a test tube held at 18 C and containing 0.2 ml. of oxalated rabbit plasma (9 parts of plasma to 1 part of 0.1 molar sodium oxalate solution) or 0.2 ml. of a 0.3% solution of bovine fibrinogen (Armour) in 0.02 molar veronal buffer, pH 7.2, containing 0.16 molar sodium chloride solution. The test tube is removed from the water bath and 0.2 ml. of recovered thrombin suspension

Preoperative and Postoperative Levels (in Units per Milliliter) of Recoverable Thrombin in Various Patients

No. Days After Operation	Patient * A	B	C	D	E
			Preoperative Levels		
	17	24	24	15	Not done
			Postoperative Levels		
1	..	..	35	..	53
2	..	..	40	..	..
3	24	..	..	48	..
4	29	..	..	24	20
5	48	44	..	33	20
6	26	31	..	40	18
7	15	37	29	26	..
8	..	37	26	..	..
9	..	44	31	..	..
10	..	..	..	37	..
11	..	..	..	29	20
12	53	..	..	48	18
13	26	..	..	29	20
14	53	..	35	48	18
15	..	..	29	..	24
16	..	..	48	..	24
17	..	..	..	31	..
19	40	..	35	..	..
20	29	..	37	..	..
21	26	..	48	..	..
24	31	..	..	..	..
25	28	..	..	..	..
26	31	..	..	..	..
27	40	..	..	..	..
31	41	..	..	..	..
33	44	..	..	..	..
34	33	..	..	..	..
38	24	..	..	..	..
42	18	..	..	..	..
46	44	..	..	..	..
47	24	..	..	..	..

* Patient disability and treatment: A: transcervical fracture of right hip; Whitman osteotomy. B: fissure in ano; resection. C: acute perforated peptic ulcer; closure of duodenal ulcer. D: chronic biliary tract disease; cholecystectomy. E: acute peritonitis due to ruptured appendix; drainage.

is blown into the tube on starting a stop watch. After mixing of its contents (with care, to avoid bubbling), the tube is held in a nearly horizontal position upon a suitable support against a screened source of light and tilted slightly until the appearance of granules, at which time the stop watch is arrested. The dilution of recovered thrombin giving a clotting time (granule appearance time) of 18 seconds with oxalated rabbit plasma is designated as one unit. A curve converting clotting times above eight seconds into units may be constructed by determining the clotting times of varying dilutions of thrombin with a constant amount of oxalated plasma or fibrinogen solution. The clotting activity with thrombin of each new batch of dried fibrinogen is determined by comparison with oxalated rabbit plasma. Suspensions giving clotting times below eight seconds are suitably diluted with other samples of recovered thrombin of known clotting times until the mixture gives a clotting time above eight seconds.

RESULTS

Normal human plasma was found to contain thrombin-antithrombin complex. The amount of thrombin recovered from the plasma of 39 presumably normal members of the staff, of different ages and both sexes, averaged 23 units per milliliter with a standard deviation of 6.1. Using Thompson's method of moving averages,[6] it was found that a level of 35 units per milliliter or above would be significantly elevated with a probability of 97.5%. No changes from normal were observed when a person was bled repeatedly at frequent intervals.

Preoperative and serial postoperative determinations are given in the table. The preoperative results in patients A, B, C, and D were within normal limits despite the underlying clinical condition. After operation a rise in recoverable thrombin took place, and the levels remained elevated for a long time. No clinical signs of thrombosis

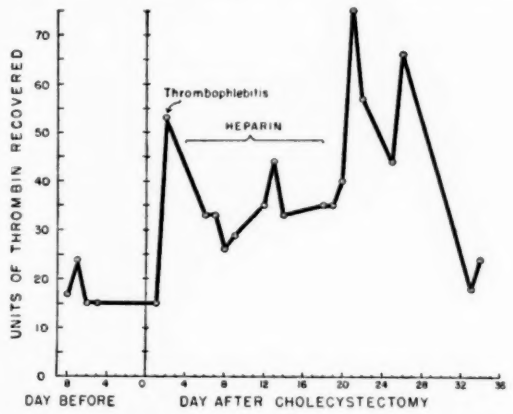

Chart showing thrombin levels in a patient before and after cholecystectomy. Note effects of occurrence of thrombophlebitis and administration of heparin.

developed in any of these patients, and their recovery was uneventful. Patients A, B, and D were afebrile throughout the postoperative course, while patient C became afebrile on the sixth postoperative day. At the time of discharge of patients B, C, and D, the thrombin level was still high. Patient A, a 66-year-old man, was still immobilized in a cast at the time of writing. The prolonged and irregular elevation of thrombin in patients A, B, C, and D, who were all middle-aged or elderly men, may be compared with the results in patient E, a 12-year-old boy with peritonitis due to a ruptured appendix. Here, too, an elevated thrombin level was found after operation, but on the fourth day the value had returned to normal and remained there throughout the postoperative course despite the fact that fever (100 to 101 F [37.8 to 38.3 C]) persisted while the incision drained and the wound granulated. The rapid return to normal in this young patient may have been due to his age.

The figure shows the preoperative and postoperative thrombin levels in a patient with chronic cholecystitis in whom popliteal thrombophlebitis developed on the second day after cholecystectomy. Thrombosis was asso-

6. Thompson, W. R.: Use of Moving Averages and Interpolation to Estimate Median-Effective Dose: I. Fundamental Formulas, Estimation of Error, and Relation to Other Methods, Bact. Rev. **11**: 115-145 (June) 1947.

ciated with a pronounced elevation of the thrombin level. The patient was subsequently given daily injections of 400 to 800 mg. of depo-solution heparin sodium. Despite the suppression of conversion of prothrombin to thrombin effected by heparin,[7] the patient still had fairly elevated thrombin levels during treatment. Soon after heparin had been stopped, the thrombin level returned to persistently high levels. A normal level was regained only by the 33rd postoperative day.

Patients with thrombosed hemorrhoids offered the opportunity of testing circulating thrombin before and after excision. In one case of thrombosed external and internal hemorrhoids, thrombin determinations on six preoperative days averaged 51 units per milliliter (highest 80, lowest 22 units). The postexcision values were 24 and 30 units. A patient with subacute bacterial endocarditis showed an elevated level, 48 units per milliliter, during an episode of developing petechiae. He had normal values (24 units per milliliter) at times when he was afebrile and asymptomatic. A patient with acute endocarditis and a temperature of 104 to 105 F (40.0 to 40.6 C) showed normal values (average, 26 units per milliliter). Postmortem examination disclosed a subaortic abscess that had ruptured into the lumen. Verrucous endocarditis, but no thrombi, was found.

Elevated values were repeatedly found in patients with chronic heart failure on rest. Therefore, in the observation of patients with symptoms of coronary occlusion, only those who had not had persistent heart failure before the coronary incident were included. In three of seven such patients, there developed an increased blood sedimentation rate, fever, leukocytosis, and electrocardiographic signs of myocardial infarction during observation. Eight thrombin determinations made after admission, but not later than the seventh day, averaged 40 units per milliliter (maximum 44, minimum 31 units). A fourth patient (44 units per milliliter) died on the second day. A posterior wall infarct was found at postmortem examination. Three other patients admitted with symptoms suggestive of coronary occlusion failed to show persistent leukocytosis and elevation of the blood sedimentation rate. They remained afebrile and their electrocardiograms showed no signs of myocardial infarction. (One of these patients had a wandering pacemaker on the second day of admission, which disappeared a week later.) Six thrombin determinations carried out immediately after admission, and not later than after the seventh day, averaged 21 units per milliliter (maximum 28, minimum 18).

A 55-year-old woman with congestive heart failure, long-standing auricular fibrillation, and a history of repeated embolisms had a thrombin value of 33 units per milliliter on admission. The following day the thrombin had risen to 44 units. Five days thereafter she contracted a fatal pulmonary embolism. A patient with cellulitis of the superficial tissues of the lower extremity associated with extensive superficial thrombosis yielded a mean value of 45 units per milliliter (maximum 57, minimum 31) in eight determinations carried out during a period of 22 days.

Elevated thrombin recovery levels were found in patients with acute biliary tract disease without jaundice (acute cholecystitis with or without elevation of serum amylase). The average value obtained in 45 serial tests on four patients was 37 units per milliliter (maximum 77, minimum 13). Normal values were obtained in patients with chronic biliary tract disease. A patient with a duodenal ulcer eroding into the pancreas (serum amylase, 325 units per cent, Somogyi fermentation method, normal 40 to 160 units per cent) had 70 units of recoverable thrombin per milliliter on admission. With clinical improvement the thrombin level gradually fell to 15 units per milliliter. In another patient with a simple peptic ulcer, normal thrombin recovery values were obtained (average of 24 units per milliliter in eight determinations; maximum 31, minimum 15).

COMMENT

The results of these observations indicate that thrombin formation is increased during disease and that the thrombin recovery test may reflect the coagulative condition of blood. The presence of recoverable thrombin in the circulation of normal persons suggests a continuous activation of prothrombin in vivo. Such slow clotting may explain the absence of hemorrhage under normal conditions and its occurrence in hypoprothrombinemic states.

An elevation of recoverable thrombin would be expected to indicate clinical conditions in which fibrin formation is increased. Increased intravascular formation of fibrin would not necessarily lead to complete obstruction of the blood vessel and thrombosis. Indeed, it may be possible that thrombin recovery also indicates the presence of small clots that do not progress to the state of causing circulatory impairment. Whether extravascular fibrin formation (as in exudates) is reflected by an increase in circulating thrombin-antithrombin complex has not been determined.

SUMMARY

Active thrombin was recovered from the thrombin-antithrombin complex found in the plasma of normal persons. An increase in circulating thrombin was observed postoperatively and in various thrombotic states and may be associated with other disorders.

7. Ferguson, J. H.: The Action of Heparin, Serum Albumin (Crystalline), and Salmine on Blood-Clotting Mechanisms (In Vitro), Am. J. Physiol. **130**: 759-770 (Oct.) 1940.

Roentgen Diagnosis of Placenta Praevia.—The diagnosis of presence or absence of placenta previa can be made with a high degree of accuracy without the use of contrast substances in adjacent pelvic viscera. Careful study of films is necessary and review of films in doubtful cases is indicated, especially if first reading is made on wet films. Films of optimum quality are essential, particularly in cases where marginal implantation is suspected. Important diagnostic signs are as follows: (1) Failure to demonstrate placental shadow in fundus of uterus. (2) Low implantation of placenta with major portion below equator of uterus. (3) Displacement of fetal head from mid-coronal or mid-sagittal plane of pelvic inlet, especially if seen in conjunction with other signs. (4) Abnormally high position of fetal head. (5) Abnormal or unusual attitude of fetus. (6) Indentation of anterior rectal wall or displacement of rectum to either side by abnormal pelvic soft tissue mass. (7) Increase in width of extrafetal intrauterine soft tissue shadow at level of symphysis pubis anteriorly or sacral promontory posteriorly. (8) Obliteration of outline of bladder on anteroposterior views, especially if unilateral.—John S. Fetter, M.D., Diagnosis of Placenta Previa Without Use of Contrast Media, *The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*, August, 1952.

THE CLEVELAND HEALTH MUSEUM'S PROGRESS TOWARD PATIENT EDUCATION

Bruno Gebhard, M.D., Cleveland

Patient education is an important part of public health education because sick persons are concerned primarily about their own health and to be concerned is the first step in learning. Patients want to know what happened to them and why it occurred. They wonder to what extent they themselves are responsible for their illness. In illness it always has been and it always will be the patient who makes some kind of first diagnosis. Usually the patient decides the time, the place, and the type of treatment to which he is going to submit himself. The educated patient, steered by his physician, is likeliest to make the right decision. Some physicians are of the opinion that health education might lead to self-diagnosis. The truth is that if a patient is unaware of any abnormality he will not take the first step: namely, to seek proper treatment. Persons born with certain tendencies will become hypochondriacs with or without health education. On the other hand, honest health education releases anxieties and encourages a more optimistic outlook. The term "laity," as commonly used, originated in medieval days, when first the clergy and later on those in law and medicine set themselves apart from the common people, then considered "uneducated." In a democracy, where professions and persons are not separate units, the word laity too often implies intellectual inferiority, despite the fact that common sense, an essential factor in education, is evenly distributed through all strata of society. Hence, reference to "lay public" will be omitted from this paper deliberately.

THE PHYSICIAN AS AN EDUCATOR

Many physicians are not aware of the fact that the term "doctor" means a teacher. It is not likely that the good old-fashioned family physician will return as the health counselor, since the old-fashioned family seems to have disappeared. Prepayment plans, necessary and good as they are, have done much to impersonalize the practice of medicine. To the specialist and the hospital, the physician's office is too often just a "referral center." Stanley R. Truman, in his excellent book "The Doctor," has elaborated this point quite clearly and concludes that "the threat of socialized medicine has awakened the medical profession from a place of self-complacency to an awareness that the people have been dissatisfied with medical care." [1]

Public health education is not identical, as too many physicians think, with public relations activities, and the latter is never a substitute for a program of health education. It is safe to state that the adult patient gets most of his health information not directly from his physician but from the printed word. The fact that a pharmaceutical house found it expedient to inform physicians through a special bulletin "What Patients Read" is proof of the wide influence popular medical articles have on patients. Physicians are the last ones to appreciate the good that reaches the public through newspapers and magazines; not all that is printed, however, is good.

The best education is still transmitted from one person to another in a heart-to-heart talk. Every physician whom patients see of their own choice has their confidence, or they would have gone elsewhere. There seems to be no end to the two general complaints: first, "Doctors will not tell you anything"; and second, "If doctors try to explain, you can hardly understand what they say." Complaints of the first order come more frequently from surgical and gynecologic patients than from others. The second group of complaints comes mostly from elderly patients, often inflicted with hearing difficulties and generally slower in their comprehension. They feel that they are not listened to with consideration and that their complaints are not taken seriously enough. The main difficulty, of course, is that elderly patients usually have much time on their hands while the busy physician has very little.

Patient Education at the Physician's Office.—Ernest Dichter, in his psychological research study of the physician-patient relationship, conducted at the request of the Committee on Medical Economics of the California Medical Association, has stressed the fact that it is important "to make the patient feel he is a participant and not only the recipient of doctor's orders." [2] Physicians are difficult patients and are not representative of the average patient; but Max Pinner and B. F. Miller's collection of autobiographical sketches "When Doctors Are Patients" has good case material on what patients expect, and seldom get, in their personal relationships with their physicians. The main objection is that the physician is inclined to underrate greatly the patient's overwhelming interest in his symptoms, thus falsely assuming that the patient always shares with him his dominating interest in diagnosis.[3] Making the patient feel like a participant is accomplished mainly by talking things over and doing them together. By the very nature of any disease, the patient is not at ease in his meetings with his physician. The situation is full of conflicts. Every person is basically responsible not only for his health but for his disease, although most patients are anxious to transfer this responsibility to the treating physician. Seen against this background, talking to patients is just as important as writing a prescription.

Enough has been said about the hard-to-understand Latinized language of the physician. The "Secretary's Letter of the Illinois State Medical Society," however, offers a new and refreshing approach: "Don't develop verbal professional isolationism . . . physicians were in-

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Director, Cleveland Health Museum.

Read before the Section on Preventive and Industrial Medicine and Public Health at the 101st Annual Session of the American Medical Association, Chicago, June 12, 1952.

1. Truman, S. R.: The Doctor: His Career, His Business, His Human Relations, Baltimore, Williams & Wilkins Company, 1951, chap. 14.

2. Dichter, E.: Doctor and Patient, Committee on Medical Economics, Los Angeles, California Medical Association, 1950.

3. When Doctors Are Patients, Pinner, M., and Miller, B. F., editors, New York, W. W. Norton & Company, Inc., 1952, p. 6.

dividuals before they opened the door to medicine; they lived as men; they talked as men. It should not be asking too much for them to remember these facts when they deal with men." [4] A forthcoming book by Dr. Stewart O. Wolf deals in great detail with this subject. Wolf gives four objectives that the physician should try to achieve:

1. To make the patient comfortable and secure.
2. To enable the patient to trust the doctor's skill and judgment, his respect for confidential material and his personal motivations.
3. To make it easy for the patient to talk freely and frankly.
4. To divert the discussion along the most pertinent and profitable lines.[5]

These objectives are much more far reaching than the usual history taking. Of major importance is the third objective. I like to call it "active listening to the patient," and it should be a real sharing of what concerns the patient. Whatever it is, talking or listening, both are time-consuming processes.

It is hard to explain why the harrassed physician is not making more practical use of such time-saving devices as the newer visual aids. To quote from the Dichter report: "The effectiveness of pictures in putting across a point is universally acknowledged. There is scarcely a medical lecturer who fails to present one or more slides or posters. These, it must be noted, are doctors explaining a medical point to doctors. Surely, if pictures are necessary to get across an academic or clinical subject to an audience of this caliber, they will be useful for a doctor explaining a medical or surgical condition to a patient. It is recommended that similar pictures and charts, and actual physical models, designed by medical artists in consultation with a psychologist, be made available to doctors by their medical association."[2] For more than 10 years, this practice has been followed in the workshops of the Cleveland Health Museum. Again and again, physicians have said that explaining birth model duplicates from the R. L. Dickinson collection to obstetric and gynecologic patients was very worth while. Desk projectors for "Kodachrome" slides take little space and are an improvement in contrast to the old-fashioned, roller-type, anatomic chart. Most commercially produced material suffers from a common pitfall: too much detail is shown, confusing the patient.

Because physicians more or less acquire their lifetime professional habits at medical school, the curriculum reformer would do well to consider the inclusion of patient education in the training of future physicians. I am fully aware of the fact that medical schools receive many such requests for the addition of various subjects, but I feel that this one is on particularly good grounds. It is interesting to note that the Long Island School of Medicine has tried a successful new experiment in the line of patient education, as reported by Irving Shapiro. Role playing by the medical students, one portraying the physician and another the student, with the entire class participating in discussion, was found helpful in improving history taking and in making the patient talk about whatever really concerned him. The students also improvised simple diagrams to show the patient what he was up against: for example, the removal of a cystic kidney.[6]

Group Education.—The advantages of group teaching have long been known to educators. Physicians are making more and more use of this active learning-participation method. The competitive spirit of the patient-students can be better utilized; the fact that the students are fellow-sufferers of obesity or diabetes, of alcoholism or of other mental disorders, brings them out of their guilt-padded isolation into a learning fellowship. Such group discussions should not be limited only to patients but extended to husbands or wives of patients, a procedure that is especially advisable in cases of mental illness. Group education will have to be tried in more outpatient departments. The field of nutrition is a good one with which to start, for there is great public interest and practically no medical specialty now concerned with various kinds of diets.

An interesting development in self-education of former patients has been advanced recently in Cleveland. Mothers who were trained in "natural childbirth" during their pregnancy joined together for regular meetings at the health museum to discuss with each other and with their respective husbands common problems of childbearing and child rearing. They have given themselves the name "Parents Unlimited." Physicians are invited for group discussions, but program planning is in the hands of the mothers, not professional persons.

Another interesting form of patient education is developing in connection with the Health Insurance Plan of Greater New York. Educational meetings for the subscribers are organized, and one attended by 300 persons was described in the *Montefiore Hospital Medical Group Bulletin* as follows: "It is unlikely that patients and doctors anywhere have been drawn so close to each other that questions regarding the detail of practice, the relations between doctor and patient and even the income of doctors, have been so freely asked and freely answered. The basic aim of such group discussion is to make the subscribers more aware of the periodic . . . health examinations for themselves and their families."[7]

Teaching the Sick.—Hospital patients should get special attention regarding information about their ills and their health care. Not all patients are articulate. Many hesitate to bring up their personal questions in the presence of third persons such as the resident intern or nurse. In a hospital there is little privacy, even for the private patient. Many persons still have a horror of hospitals, considering them to be what H. E. Sigerist, in "When Doctors Are Patients," has termed: "that blend of penitentiary and third-class hotels."[3] To be in a hospital is to be in a world apart, and for many persons it is a very strange world at that. Most persons neither are born nor do they die in their own homes, but in hospitals. Physicians have a special obligation to make these two events of life an important part of their own thinking and of their thinking in dealing with patients. Patient education in hospitals should be carried on in an organized fashion; the modern hospital cannot leave it to the chance action of physicians and nurses. Concerning the beginning of life, classes for expectant mothers are a good supplement

4. Secretary's Letter of the Illinois State Medical Society, Health Officers News Digest **16**: 27 (Dec.) 1951.
5. Wolf, S. O.: Talking with the Patient, abstracted, Current Med. Digest **19**: 21-22 (Jan.) 1952.
6. Shapiro, I.: Doctor Means Teacher, J. M. Educ. **26**: 125-129 (March) 1951.
7. Have You Heard? Montefiore Hospital Medical Group Bulletin 16, 1951-1952.

to patient education by the physician; and, whenever possible, expectant fathers should be included in such a program.

Patient education in groups is most effective when planned and organized by a person familiar with educational procedure. Talks, films, demonstrations, and exhibits are the main media. Physicians might get assistance from professionally trained persons such as a health educator, hospital librarian, or staff teacher at the hospital's school of nursing. An over-all committee should decide on the general policy of so new a venture. Another prerequisite for a successful educational program is direct in-service education of staff and board members; without in-group understanding a patient-education project would indeed be short-lived. Some hospitals have already developed plans for practical methods of patient education. A beginning was made before World War II, when health exhibits were displayed in outpatient departments and other central locations within the Johns Hopkins School of Medicine.

The new Lankenau Hospital in Philadelphia is the first to provide in its building nearly 5,000 sq. ft. of space for a permanent health museum, located next to the general waiting room. It is closely connected with an auditorium where public lectures and films will be regular features. Dr. Edward Bortz, medical director, and Donald Gay, former hospital administrator, have been the motivating forces in this enterprise. The Cleveland Health Museum acts as a consultant, and many of its exhibits will be duplicated for the new Lankenau Hospital museum. These exhibits will set forth a sound presentation of the human body, with stress on ways and means of health conservation and on periodic health examinations. Special attention will be given to the new field of geriatrics. Focal point of the museum will be the pertinent facts of human reproduction as a basis for healthful family life. Not only patients and their relatives but also school classes and additional groups can arrange to view the exhibits. It has taken quite some time from the Civil War days of the Army Medical Museum, with its pathological specimens, to the health teaching exhibits in a modern hospital. Just as medical teaching is always changing, so health education for the public has to be molded according to the needs of those who require it most: the patients.

PROCEDURES

Patients live not as individual persons but as family units, and families make up the community. In an earlier paper, I discussed the practice of the Cleveland Health Museum in helping physicians play their part in public health education.[8] A museum, or any other teaching institution, is not made up of the buildings or its staff and exhibits but the working philosophy and the educational policy. Formerly, museums of hygiene or medical museums for the public were built around the subjects of medical science and hygiene was seen as an organized defense against environmental forces: an outgrowth of the bacteriological discoveries of the last century. Today, in developing the Cleveland Health Museum, thought is centered around the normal growth and development of the human life from birth to old age. Most persons are healthy most of the time, and it is better health that is wanted, not just freedom from disease.

Human Stages of Learning.—Not at all times of their lives do persons have an interest in their bodies; but, out of experimentation, five learning situations for health education have been crystallized:

1. Childhood.—In bringing up a child, health is the primary concern of every mother. Eating and elimination, play and sleep, and work and rest are fundamental in the development of the human personality, which, according to the psychologist, is formed in the first five years of life. The physician is becoming more and more accepted as an advisor in health matters of growth and development for the young child. The child who shows normal curiosity about his body is easily satisfied by an understanding mother.

2. Adolescence.—Before the development of interest in the other sex, there is an increased awareness of one's own bodily changes and appearances. Physicians, including school physicians, have been reluctant to take on the field of sex education. In evidence of this, consider these verbatim questions, typical of the inquiries with which the museum instructors are confronted every day:

Do fathers have a sickness while their wives are pregnant?
Why do women's stomachs rise?
Why does a mother have pains when the baby is born?
Why do some babies come out in seven months?
Is there any other way to start a baby?

These particular questions, elementary as they may seem, actually were asked by senior high school students. Film showings on human reproduction and visits to the "Wonder of New Life" room invariably provide the sincerely sought answers.

3. Adulthood.—Men and women who might not care about their own health are willing to change their habits when, as a married couple, they expect their first child. Classes for expectant mothers, and fathers as well, are one of the best vehicles for health education. Physicians should stimulate the organization of such classes.

4. Old Age.—Aging naturally brings with it an interest in health matters. Diseases of old age, beginning with obesity, heart disease, cancer, and diabetes, cannot be controlled by public health methods but need an individual approach. The physician has a special obligation not only in this line of health counseling but also in group learning. In June, 1951, the health museum cooperated with the Cleveland Division of Health, the Welfare Federation, and other agencies to conduct a well-attended three day institute at the museum, the Conference on Health and Happiness for Older People. Delegates from the 50 Golden Age and Live Long and Like It clubs in Cleveland engaged in active discussion following five key addresses. Topics were decided on by the Committee on Older Persons:

My Back Aches and My Feet Hurt, Robert M. Stecher, M.D., president of the Cleveland Health Museum, and staff physician, City Hospital, Cleveland.

I Am Nervous; You Make Me Nervous, Alfred Bochner, M.D., staff physician, Lakeside Hospital, Cleveland.

Adjustment to the Older Years, Clark Tibbitts, chairman, Committee on Aging and Geriatrics, Federal Security Agency, Washington, D. C.

I Have Trouble with My Heart, Harold Feil, M.D., staff physician, Mt. Sinai Hospital, Cleveland.

Thou Shalt Not Grow Old, Rabbi Armond Cohen, Park Synagogue, Cleveland.

8. Gebhard, B.: Community Health Education by the Medical Profession from Medicine Show to Health Museum, J. A. M. A. **127**: 506-508 (March 3) 1945.

5. Period of Poor Health.—The period that was described in the beginning of the paper.

Exhibits at the Museum.—The content of patient education has a great scope and might include practically all phases of life; there are, however, some basic considerations that should always be included. The rules of healthful living must conform with the laws of biology and those of hygiene, which actually are nothing less than applied biology. Since health is an extremely personal affair and more or less bound to the individual person's physical and mental make-up, a certain minimum knowledge of the human body is necessary. Only when there are no "biologically illiterates" can everyone discriminate between sound and unsound advice in health matters.

The museum exhibits include synoptic presentations on the different organic systems, with "Juno," the talking transparent woman, the best-known feature. In the intimate setting of the science theater, her 15 minute demonstrations highlight museum visits by both the average and the sophisticated visitor.

About equal in attracting and holding interest are the exhibit rooms on "The Wonder of New Life," dealing with human reproduction, and "Food for Health." Almost 300 school groups, not only from Greater Cleveland but from all of Northern Ohio, make use of the special instruction classes conducted by members of the education department. Often included are parochial school groups; but the diversity of groups is best shown by one of the typical daily attendance records:

April 30, 1952

Group Number	Group	No. of Visitors
(296)	Hough School (dental hygiene lesson)	87
(297)	Rawlings Junior High School	35
(298)	Liverpool (Ohio) Local School	34
(299)	Rabbinical College of Telshe	20
(300)	Heart of the Home	16
(301)	Warren (Ohio) Township School	54
(302)	Diabetes League of Greater Cleveland	97
	Individual visitors (not with groups)	114
	Total visitors for day	457

Total Visitors Since Jan. 1, 1952: 23,709

Film Showings (no. of times this day)

Human Reproduction (2)	Body Fights Bacteria (1)
Human Growth (1)	Choose to Live (1)
Endocrine Glands (1)	Planning for Good Eating (1)
Nose, Throat, and Ears (1)	Human Body (1)

Message to Women (1)

More school visits (1951 showed a 28% increase over 1950) mean more family visits: "Nearly 9,000 youngsters (during 1951) saw films of every description, heard Juno's fascinating story and received instruction on many health subjects. Interest aroused in these young people was transmitted to their brothers and sisters, their mothers and fathers, at home. Many were the families who returned to the Museum with Joan or Tommy on a weekend to share, as a family unit, the exhibits and program Joan or Tommy had experienced with classmates." [9]

Of necessity, present staff and physical facilities enforce a considerable limitation on our attendance (60,000 per year); but it is of interest to note that these visitors represent a self-selected audience that attends for more than idle curiosity. The museum outgrew its first home five years after opening, and, in 1946, larger quarters became available. The first special exhibit dealt with the subject "Who Is Your Doctor?" Since only two-thirds of the population rely on conventionally trained physicians for their services, emphasis in this exhibit was on the training of the physician and the work of the general practitioner. Because the making of models is one of the main features of the workshop, it naturally followed that models showed the different diagnostic procedures: what the physician actually sees when he looks into the patient's eye, ear, and stomach or when he roentgenographs pregnant women or brain waves of a child in whom epilepsy is suspected. A large tableau "Not All Doctors Are Physicians" tried to help the visitor differentiate between the D.M. and M.D., between the D.O. and D.D.S.

A permanent exhibit, "Want to Be a Doctor?", consisting mainly of units loaned by the American Medical Association, pictorialized, with many push-button models, the field of premedical studies and clinical courses. The Academy of Medicine of Cleveland frequently enlists museum workmanship for special projects entailing public participation. Such was the case in 1942 with the exhibit "Appendicitis"; and this year a special exhibit was designed for suburban health fairs, calling attention to 24 hour telephone service, new medical insurance plans (Medical Mutual of Cleveland), and other academy services. In recognition of "the value of the Museum to Cleveland as an educational and health project," [10] the academy presented the entire museum story in a special issue of their bulletin. In substance, it was a chronology from the inception in 1936 to present day activities.

A Force in the Community.—A museum naturally emphasizes the visual forms of education, but this does not exclude other forms of communication. Various A. M. A. program packages have been scheduled frequently with the local radio stations; the series "Doctor's Orders" was particularly well received. Live radio and television scripts are now in preparation, and the newsletter *Tone* keeps members and friends informed about current and coming events. A new series of health guide booklets for general consumption was launched this year with the publication of "Juno—Symbol of All Women"; others will be concerned with human reproduction and with the latest exhibit "We the People," which dramatizes 1950 census figures on a "10-finger" basis.

From time to time, the auxiliary medical services are portrayed. An exhibit "What Nurses Do," sponsored by the Ohio State Nurses Association, attempted to help in the reinstatement of student nurses. Schools of nursing, including those for practical nurses, take advantage of the guided tours and use the extensive health film library. Occupational therapists use the museum each year as the site for a comprehensive display showing what patients can do with their hands in protracted illness and during their days of convalescence.

That the general public appreciates these activities is evidenced by the change in the composition of museum membership. In 1940, two thirds of the total membership (800) was of a professional nature, primarily physicians and dentists. As of May 1, 1952, the membership, with minimum dues of $10.00, had nearly tripled (2,200). Of major importance is the fact that this growth was effected

9. Doyle, W. G.: Education Department Has Slow Winter, Busy Spring, Tone **13**: 2 (March-April) 1952.

10. The Health Museum, editorial, Bull. Acad. Med., Cleveland **36**: 12 (Aug.) 1951.

by an increase in nonprofessional persons who now comprise nearly two-thirds of the total.

It is natural that this progressive new endeavor in health education gets its due share of criticism. Just as the praise received is not always based on merit, the museum is not always responsible for the blame it gets. It seems that it is accused oftener of sins of omission than of those of commission. "Why doesn't the museum do more about alcoholism . . . blood diseases . . . cancer . . . diabetes . . . epilepsy," is becoming a standard question. Timely "Exhibits of the Month" deal with those subjects and with medical specialties like allergy and radiology. A proportionate section of the exhibits has always embraced dental health; duplicates of a giant plastic tooth are now housed in the Franklin Institute and the Boston Museum of Science.

Being basically a museum of science, it tries to steer clear of anything political or professional that is either controversial or has even the faintest hint of propaganda. Nevertheless, the exhibit material was quoted as an "Exhibit" in the legal oleomargarine discussion. Lawyers borrow charts for demonstration in courts of malpractice and also for workmen's compensation proceedings. Emphasis on family life education, embarked on in 1946 when the world-famous Dickinson models on human reproduction were acquired, has brought the museum many friends and grateful parents and also, as was to be expected, some criticism. The strictly objective form of presentation, helped by artistic display, made it possible to show facts that might not be allowed to appear in print.

Throughout its 12 years of development, the health museum has proved to be a proper place for individual person, family, and group health education. While the formidable name "museum" might scare some persons away, it also guarantees a certain selectivity in the type of its visitors; they have a willingness to learn that should not be underestimated. A museum assures the visitor that the presentation of subject material is on a scientific basis and protects him against selfish exploitation.

Evaluation.—Patient education with the 60,000 yearly visitors at the Cleveland Health Museum has stressed family life education, school health, and the "Live Long and Like It" movement. Evaluation of this 12 year program is difficult at best, because most of the values involved are intangible. Perhaps the best measure is the increase in annual attendance: from 30,000 visitors in 1941 to nearly 60,000 in 1951. Certainly this represents public acceptance of pleasing dimensions, as does the increase in membership from 800 in 1940 to 2,200 at present. On the other hand, if the ratio of "services requested" to "services rendered" gives some indication of the effectiveness of any agency not incorporated for profit, it is falling behind: for the activity income is limited by the policy of free admission.

There is no doubt that the 600 member-physicians on many occasions are aware of the health museum in their dealings with patients. It has been written in a previous paper: "One of the underlying goals of the Cleveland Health Museum's many and varied activities is perfect understanding and faith between doctors and their patients. For this reason, Museum exhibits go beyond biology into personal health, with special emphasis on the 'positive' rather than on the 'negative' side of living." [11]

Based on an annual attendance of 60,000 visitors who spend an average of 1½ hours at the museum, the visiting hours amount to 90,000 yearly. If the 2,000 practicing physicians in the metropolitan area would divide this load into individual health counselling and lecturing to women's groups and civic organizations, each one would have to take on 45 museum visiting hours, or virtually the equivalent of a full work week.

From a more general viewpoint, the value of a health museum was pointed out by a colleague from the British Isles who had spent some time with the museum: "Only the patent medicine advertisers have followed this line before—they to prepare the public's mind for the inevitable mysterious illness, and you to prepare the public's mind by knowledge. It may very well be, if psychobiological concepts are at all true, that by conditioning, health museums may alter the receptive terrain and, quite apart from their educational value, may reduce the susceptibility to various kinds of illness, notably those involving the autonomic and cardiovascular systems."

This observation by the British visitor confirms what has been said all along: seeing is both believing and relieving. To see makes one believe; to see the workings of the human body in "do-it-yourself" three dimensional exhibits relieves the patient of the fears concomitant with disease and illness, and, over and above that, it arouses admiration for the miracle of the human body. Epitomizing the reason for the existence of the Cleveland Health Museum is this wall inscription from St. Augustine: "Man wonders over the restless sea . . . the flowing waters . . . the sight of the sky . . . and forgets that of *all* wonders, man himself is the most wonderful."

SUMMARY

1. The patient who visits or calls a physician is the first diagnostician, right or wrong, of his own illness; therefore, patient education is the most important part of public health education.

2. The initiative and practice of patient education rest with the individual physician. He should use modern visual aids to make his person-to-person relationship with the patient more effective; he should take the lead in organizing programs of patient education, not only in schools and hospitals but on a community-wide basis, with health-teaching exhibits, lectures, and films as the framework.

3. All citizens, young and old, are prospective patients; to sensitize them is the function of the Cleveland Health Museum. Through visual material, group discussions, and mass media, this museum has personalized health, laying stress on the positive elements of family life, school life, and life of older persons.

4. Just as the physician can be called too late, patient education can be delayed too long. As a result, patient education at the health museum begins with the child. This comprehensive program has won appreciable acceptance by the public, most of whom are healthy most of the time and, consequently, seek better health rather than just freedom from disease.

8911 Euclid Ave.

11. Stecher, R. M., and Gebhard, B.: The Doctor and the Cleveland Health Museum, Practitioner **167**: 275-280 (Sept.) 1951.

CLINICAL NOTES

EFFECT OF SEROTONIN ON BLOOD PRESSURE AND LACK OF EFFECT OF ANTIMETABOLITE

Tom D. Spies, M.D.
and
Robert E. Stone, M.D., Birmingham, Ala.

For several years we have determined the blood pressure of patients with nutritive failure when they entered the nutrition clinic of the Hillman Hospital. We have found great variation in the blood pressure readings, ranging from systolic pressures of around 70 to pressures that cannot be read on an ordinary sphygmomanometer. In general, persons with severe nutritive failure tend to have a systolic and diastolic blood pressure below average, and, when the nutritive failure is corrected and they begin to lead a more energetic life, the blood pressure tends to increase.[1]

In 1868 Ludwig and Schmidt [2] described a vasoconstricting agent that occurs in the serums of mammals, and it occurred to us that this agent, or some such substance, might be affected by nutritive failure and thus account for the decrease in blood pressure readings of certain of our patients. This thought led us to ask ourselves: Could it be that patients with clinical hypertension produce an abnormally large amount of this vasoconstricting agent, or could it be that hypertensive persons do not destroy this vasoconstricting substance as promptly as the average person? Could it be that patients with low blood pressure produce less than the normal amount of this agent or destroy it more rapidly than other persons?

A possible way to answer these questions was suggested when Rapport [3] isolated from beef serum a very active vasoconstrictor. He found that this material was composed of sulphuric acid, creatinine, and an indole base. The indole base was identified as 5-hydroxytryptamine, and is called serotonin (fig. 1). Recently serotonin has been synthesized by two groups of investigators,[4] and we have obtained it in synthetic form for study.

The patients selected for this study were comprised of persons with hypertension, persons with hypotension, and persons with normal blood pressures. Although they had been under observation for a number of years and were accustomed to our ways of working with them, we decided to spend one or more days giving them injections of sterile saline solution and determining their blood pressures frequently. Then, without any change in technique, we injected intravenously from 0.25 to 5 mg. of serotonin dissolved in saline solution in 5 to 300 seconds. In every person when 0.5 mg. or more was injected, there was a prompt and sharp rise in systolic and diastolic blood pressure, as shown in figure 2. Concomitant with the increase in blood pressure, the patients felt mild cramping pains or fullness in the abdomen, a sensation of fullness in the chest, peculiar sensations and dizziness in the head, and tingling of the extremities; then the blood pressure returned to the baseline level in 10 minutes or less. These observations were reproducible; some patients were given a series of injections of 1 or more milligrams two or three hours apart until they had received as many as six injections of serotonin, and each time there was a rise in systolic and diastolic blood pressure when the material was injected.

Recently Woolley and Shaw,[5] using ring-shaped segments of sheep carotid artery, have shown that 2-methyl-3-ethyl-5-aminoindole tends to decrease the restrictive effect of serotonin; that is to say, there is an antagonistic effect between serotonin and this other indole compound that is so similar in structure (fig. 1). Thus, we can consider this compound an antimetabolite to serotonin. The natural questions arise: Is this antimetabolite safe to give to human beings? Will it show the same antagonistic effect to serotonin in human beings as it does in sheep carotid artery?

After making a number of observations as to the relative safety of 2-methyl-3-ethyl-5-aminoindole, we began administering it intravenously in minute amounts to all the persons with high blood pressure, low blood pressure, and normal blood pressure who had received serotonin. Later, we gave 2-methyl-3-ethyl-5-aminoindole in 5 mg. amounts and then in 20, 30, 40, 50, and 100 mg.

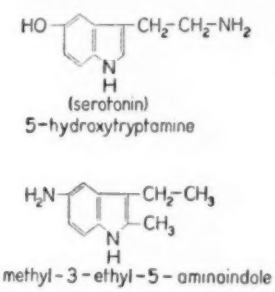

Fig. 1.—Structures of serotonin and the potential antimetabolite, 2-methyl-3-ethyl-5-aminoindole.

amounts. The injection of this material was followed by some, but not serious, disturbances.

Three patients with hypertension, three with hypotension, and two with normal blood pressures each received 300 mg. of 2-methyl-3-ethyl-5-aminoindole intravenously over a period of eight hours for two or three days, but in no person did the blood pressure decrease below the baseline reading. (At this point no more material

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Clayton Foundation Fellow (Dr. Stone).

This study was supported by a grant from the Clayton Foundation for Research.

The synthetic serotonin (5-hydroxytryptamine), the synthetic 2-methyl-3-ethyl-5-aminoindole, and the 2-methyl-3-ethyl-5-nitroindole were obtained through Dr. A. E. Osterberg of the Abbott Laboratories, North Chicago, Ill.

From the Department of Nutrition and Metabolism, Northwestern University Medical School, Chicago, reporting studies in Nutrition and Metabolism at the Nutrition Clinic, Hillman Hospital, Birmingham, Ala.

1. Spies, T. D., and Stone, R. E.: Hypotension Associated with Nutritive Failure, Proc. Soc. Exper. Biol. & Med. **72**: 368, 1949.

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was available.) All the patients with hypertension volunteered that they felt more relaxed. In one patient headache, which had been present for over a month, disappeared and did not return over a period of several days.

After giving this so-called antimetabolite until we had no more material, we tested with serotonin as before, and the patients again had a prompt increase in blood pressure and some minor disturbances, thus showing that in the dosage given the 2-methyl-3-ethyl-5-aminoindole had not blocked the effect of the serotonin.

SUMMARY AND CONCLUSIONS

1. The injection of synthetic serotonin (5-hydroxytryptamine) intravenously in amounts of 0.5 mg. or more in persons with normal blood pressure, with low blood pressure, and with high blood pressure was followed by a

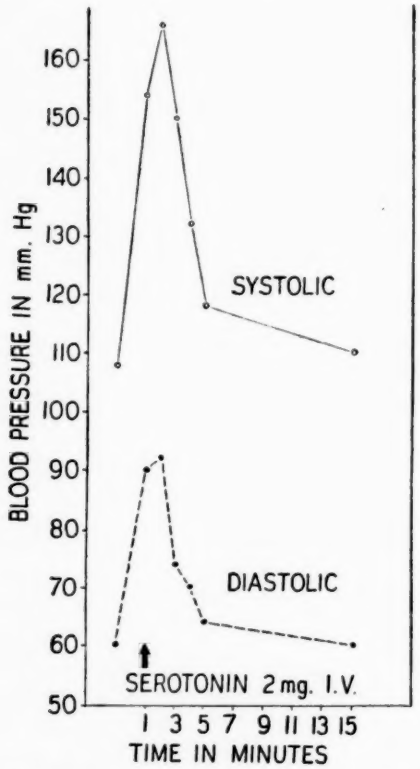


Fig. 2.—Blood pressure response following injection of serotonin.

prompt and definite increase in systolic and diastolic blood pressure. Often associated with the increase in blood pressure were some abdominal pain, a sensation of fullness in the chest, peculiar sensations and dizziness in the head, and tingling of the extremities.

2. The potential synthetic antimetabolite of serotonin, 2-methyl-3-ethyl-5-aminoindole, seems to be tolerated rather well in persons with normal blood pressure, with low blood pressure, and with high blood pressure. We have given as much as a total of 300 mg. within eight hours for two or three days. Following the injections of 2-methyl-3-ethyl-5-aminoindole, the blood pressure readings did not go below the baseline readings. The patients with hypertension stated, however, that they felt much more relaxed, and in the only patient with hypertensive encephalopathy headache disappeared. It is interesting to note that when serotonin was given after the patients had received injections of 2-methyl-3-ethyl-5-aminoindole, the so-called antimetabolite did not block the effect of the injections of serotonin.

3. As a part of another study on the effect of oral administration of the potential antimetabolites of serotonin, one patient with hypertension was given 22 gm. of synthetic 2-methyl-3-ethyl-5-nitroindole orally over a period of eight days. During this period no change in blood pressure occurred. When the last dose of this compound was given, we administered 0.5 mg. of serotonin intravenously. The response to serotonin was similar to that shown in figure 2, indicating that under the conditions of the study this compound did not block its effect.

COUNCIL ON PHARMACY AND CHEMISTRY

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies. A copy of the rules on which the Council bases its action will be sent on application.

R. T. STORMONT, M.D., *Secretary.*

Selenium Sulfide.—Selsun Sulfide (Abbott).—F.W. 143.09.—Selenium sulfide is a mixture of crystalline selenium monosulfide and solid solutions of selenium and sulfur in an amorphous form, part of which could have the formula Se_nS_m where n plus m equals 8.

Actions and Uses.—Selenium sulfide is employed only externally as a liquid suspension for application to the scalp in the treatment of seborrheic dermatitis and the control of seborrhea sicca (dandruff). It may be useful to a lesser extent in the management of psoriasiform seborrhea, seborrhea oleosa, acne vulgaris and juvenilis, and atopic eczema. It is not effective against ringworm of the scalp caused by Microsporon audouini.

Selenium sulfide is absorbed through the skin to only a slight degree. Experimental studies indicate that the amount absorbed, when applied as recommended below, is not much greater than the traces which may be present in the average diet. Selenium sulfide is highly toxic if taken orally and patients should be instructed to wash their hands and clean beneath the finger nails to remove all traces of the drug following each external application. The danger of accidental poisoning should be emphasized, and each patient should be warned to keep the drug out of the reach of children. Patients should be advised not to repeat applications unless directed by the physician. External use has not so far revealed any case of intoxication attributed to selenium sulfide. Sensitivity reactions which have been reported in some instances are believed caused by the detergent, alkyl aryl sodium sulfonate, which is present in the commercially available suspension of the drug, although sensitivity to the drug itself may rarely be encountered.

Dosage.—Selenium sulfide is applied externally as a suspension containing 2.5% of the agent. For application to the scalp, the hair should be shampooed first with ordinary soap and rinsed. From 5 to 10 cc. of the suspension is then applied by light massage with a small amount of warm water to make a lather. This is allowed to remain in contact with the scalp briefly, then rinsed and the application repeated. The agent should remain in contact with the scalp for a total of at least five minutes. The second application should be followed by three or four rinses to remove all traces of the agent. It is recommended usually that such applications be made twice weekly for two weeks and then once weekly or less often as indicated.

Tests and Standards.—

Physical Properties: Selenium sulfide is a dull reddish orange to dull brown, amorphous powder. It is odorless, or has a slight sulfide odor, is tasteless, and decomposes at about 100°. It is practically insoluble in water and organic solvents. Selenium sulfide reacts with aqua regia to give a clear solution.

Identity Tests: The yellow precipitate of free sulfur and the red precipitate of free selenium, both produced during the assay for selenium described later, serve to identify these elements in selenium sulfide.

Purity Tests: Place about 50 mg. of selenium sulfide in the cup of the lower (or hot) electrode of an arc spectrograph. Arc the sample to completion using 13 amp. D.C. on a dead short. Develop the plate in the usual manner. Compare the most sensitive lines for the elements with lines in the spectrum of a standard powder containing copper, lead, selenium, and tellurium in concentrations of 0.1% in a carbon matrix. The concentration of copper, lead, and tellurium in the sample is less than 0.1%.

Heat to 50° about 1 gm. of selenium sulfide in 12 ml. of water and allow the suspension to cool to room temperature. Filter the mixture. Prepare a solution (0.163 μg/ml.) of selenious acid containing the equivalent of 1.0 μg of selenium in 10 ml. To 10 ml. of standard and 10 ml. of the filtrate in test tubes, add 0.5 ml. of sulfuric acid and enough bromine T.S. to make the solution brown, then discharge the color with a few drops of formic acid. Add 5-10 mg. of thiourea and heat the mixture in a boiling water bath for 10 min. Allow the test tubes to stand for 1 hour at room temperature: the solution of sample shows no more turbidity than the standard, corresponding to not more than 1 ppm of selenium from soluble selenium compounds.

Weigh about 3 gm. of selenium sulfide into a tared porcelain crucible, ignite at red heat until the selenium appears to be completely driven off, and cool and weigh the crucible: the amount of nonvolatile matter is not greater than 0.3%.

Assay: (Selenium) Accurately weigh about 0.1 gm. of selenium sulfide into a 250 ml. volumetric flask. Slowly add from a buret 25 ml. of red fuming nitric acid. Mix the contents of the flask frequently during the addition. Digest the mixture on a steam bath until no particles of selenium sulfide are visible among the lighter sulfur particles (5-60 min.). Cautiously fill to the mark with water. Cool to room temperature and readjust the volume. To a 25 ml. aliquot of the diluted digestion mixture, add 10 gm. of urea and 35 ml. of water, and bring to boiling. Cool in an ice bath and add 1 gm. of potassium iodide. At this point a dull reddish brown color appears and the solution becomes opaque, due to the formation of colloidal selenium. Titrate the mixture immediately with 0.02 M sodium thiosulfate. Each milliliter of 0.02 M sodium thiosulfate is equivalent to 0.0003958 gm. of selenium and to 0.0007155 gm. of selenium sulfide in the aliquot. The amount of selenium present is not less than 52.0 nor more than 55.5%, equivalent to not less than 94.2 nor more than 100.6% of selenium sulfide.

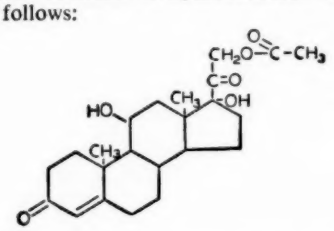
Dosage Forms of Selenium Sulfide

SUSPENSION. *Assay:* (Selenium Sulfide) Determine the density of the suspension. Accurately weigh into a tared 125 ml. Erlenmeyer flask an amount of suspension equivalent to about 0.1 gm. of selenium sulfide. Proceed as directed in the assay for selenium in the monograph for selenium sulfide starting with, "Slowly add from a buret 25 ml. of red fuming nitric acid." Each milliliter of 0.02 M sodium thiosulfate is equivalent to 0.0007155 gm. of selenium sulfide. The amount of selenium sulfide is not less than 90.0 nor more than 110.0% of the labeled amount.

Abbott Laboratories, North Chicago, Ill.

Suspension Selsun Sulfide: 118.3 cc. bottles. A buffered, stabilized suspension containing a detergent and 25 mg. of selenium sulfide in each cubic centimeter.

Hydrocortisone Acetate.—Hydrocortone Acetate (Merck).—17-Hydroxycorticosterone-21-acetate.—$C_{23}H_{32}O_6$.—M.W. 404.49.—The structural formula of hydrocortisone acetate may be represented as follows:



Actions and Uses.—Hydrocortisone acetate has the same qualitative metabolic and therapeutic effects as cortisone acetate. It has the added advantage over cortisone acetate of causing less irritation and promoting more prolonged and intense local effect when injected into the intra-articular spaces affected by rheumatoid and osteoarthritis. Local relief from pain and stiffness in the area of the injected joint usually occurs within 24 hours and persists for 72 to 96 hours or longer. Intra-articular injection should be performed only into actively inflamed joints; treatment of ankylosed joints is valueless. The practical limitations of intra-articular injection restrict the use of this method of treatment to a few actively inflamed joints at any one time. Articular joint temperature is decreased and the total cell count of the synovial fluid is reduced following treatment.

Maintenance of sterile procedure is essential. Intra-articular injection should not be attempted by those unfamiliar with the anatomic relationships of the joints involved.

When injected systemically, hydrocortisone acetate is capable of producing the same side-effects as cortisone acetate. However, when injected intra-articularly, systemic side-effects have not been observed.

Dosage.—For intra-articular injection the amount to be injected and the interval between injections varies with the degree of inflammation, the size of the involved joint, and the individual response of the patient. Small joints usually require 5 to 10 mg. Larger joints require 15 to 37.5 mg., repeated when symptoms recur.

Tests and Standards.—

Physical Properties: Hydrocortisone acetate is a white, odorless solid, m.p. 218-223° (with decomposition). It is very slightly soluble in ether and practically insoluble in water. The amounts which dissolve in the following solvents to form 100 ml. of solution are: 0.45 gm. in alcohol and 0.73 gm. in chloroform.

Identity Tests: Dissolve about 25 mg. of hydrocortisone acetate in 10 ml. of alcohol and add 15 ml. of a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid: a red precipitate forms.

The specific rotation, $[\alpha]^{25}_D$, of a solution containing 0.1 gm. of hydrocortisone acetate in 25 ml. dioxan is + 151 to + 166°.

Place a few crystals of hydrocortisone acetate on a slide and dissolve in a few drops of chloloform. Allow the solvent to evaporate and inspect the crystals under the microscope: they are small, isolated crystals *(distinction from cortisone acetate, which crystallizes in radiating rods).*

Add 2 ml. of sulfuric acid to about 10 mg. of hydrocortisone acetate in a test tube: the solution is brownish red by transmitted light and shows a strong yellowish green fluorescence by reflected light *(difference from cortisone, which gives a yellow solution that does not fluoresce).*

A 0.001% solution, prepared as described in the spectrophotometric assay for hydrocortisone acetate, exhibits an ultraviolet absorption maximum at about 242 mμ [specific absorbancy, E(1%,1 cm.), about 390].

Purity Tests: Dry about 1 gm. of hydrocortisone acetate, accurately weighed, over phosphorus pentoxide for 18 hours: the loss in weight does not exceed 1.0%.

Char about 0.1 gm. of hydrocortisone acetate, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until the evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 0.1%.

Assay: (Hydrocortisone Acetate) Prepare a 0.001% solution of hydrocortisone acetate as follows: Transfer to a 100 ml. volumetric flask 0.1 gm. of hydrocortisone acetate, accurately weighed, fill to the mark with methanol, and mix. Transfer to a second 100 ml. volumetric flask 10 ml. of this solution, fill to the mark with methanol, and mix. Transfer to a third 100 ml. volumetric flask 10 ml. of this last solution, fill to the mark with methanol, and mix. Spectrophotometrically determine the absorbancy in a 1 cm. quartz cell at 242 mμ, using methanol as a blank. The concentration of hydrocortisone acetate in the solution in mg./ml. = absorbancy ÷ 39.0. The amount of hydrocortisone acetate is not less than 95.0 nor more than 105.0%.

Dosage Forms of Hydrocortisone Acetate

SUSPENSION. *Physical Properties:* The pH of the suspension is 5.5-7.5.

Identity Tests: Add 2 ml. of sulfuric acid to a volume of suspension equivalent to about 5 mg. of hydrocortisone acetate: the solution is brownish red by transmitted light and shows a strong yellowish green fluorescence by reflected light.

The suspension, diluted as directed in the spectrophotometric assay for hydrocortisone acetate, shows an absorption maximum at about 242 mμ.

Assay: (Hydrocortisone Acetate) Transfer to a 50 ml. volumetric flask a volume of suspension, accurately measured, equivalent to about 50 mg. of hydrocortisone acetate. Fill to the mark with methanol and mix. Transfer 10 ml. of this solution to a 100 ml. volumetric flask, fill to the mark with methanol, and mix. Transfer to a second 100 ml. volumetric flask 10 ml. of this last solution, fill to the mark with methanol, and mix. Spectrophotometrically determine the absorbancy in a 1 cm. quartz cell at 242 mμ, using methanol as a blank. The concentration of hydrocortisone acetate in the solution in mg./ml. = absorbancy ÷ 39.0. The amount of hydrocortisone acetate is not less than 90.0 nor more than 110.0% of the labeled amount.

Merck & Co., Inc., Rahway, N. J.

Suspension Hydrocortone Acetate: 5 cc. vials. A saline suspension containing 25 mg. of hydrocortisone acetate in each cubic centimeter. Preserved with 0.9% benzyl alcohol.

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION
535 N. DEARBORN ST. . . . . CHICAGO 10, ILL.
Editor . . . . . AUSTIN SMITH, M.D.
Associate Editor . . . . . JOHNSON F. HAMMOND, M.D.
Editor for Medical Literature Abstracts . GEORGE HALPERIN, M.D.

Subscription price . . Fifteen dollars per annum in advance
Cable Address . . . . . "Medic, Chicago"

GROWTH HORMONE AND CARBOHYDRATE METABOLISM

The various phases of carbohydrate metabolism, namely, the oxidation of sugar to carbon dioxide and water and its conversion to fat, glycogen synthesis, and the new formation of sugar from protein and possibly fat, are all under hormonal control. The importance of the islands of Langerhans, the adrenal medulla, the adrenal cortex, and the thyroid in carbohydrate metabolism are well recognized. Great progress has been made in establishing both the conditions that determine and the factors that regulate the secretory activity of these organs as well as the exact role of their various hormones in the chain of intermediary reactions involved in carbohydrate metabolism. Recent work has shown that still another endocrine factor must be added to the above list, namely, an anterior pituitary factor other than corticotropin, most probably growth hormone or some other hormone closely linked with it.

The relation of the anterior pituitary to carbohydrate metabolism originally was demonstrated by the classical work of Houssay,[1] in which removal of the hypophysis ameliorated the disturbances induced in the dog by pancreatectomy. Furthermore, the administration of extracts of the anterior lobe was found to produce hyperglycemia, glycosuria, and ketonuria in the normal dog.[1] Later, Young succeeded in producing permanent diabetes mellitus in dogs by prolonged injections of anterior pituitary extract. Subsequent examination of the pancreases of his animals revealed degeneration of the islands of Langerhans.[2] Although the diabetogenic action of anterior pituitary extracts can, in part, be attributed to their corticotropin content, it was shown that, for the most part, this activity was due to another factor independent of corticotropin, since the diabetogenic effects of these extracts were not eliminated after both adrenal glands had been ablated.[1]

With the isolation and production of a purified growth hormone, the study of this hormone's effect on carbohydrate metabolism received new impetus and was begun simultaneously in several laboratories. Young [3] and Campbell [4] and their associates, respectively, produced diabetes with this hormone in normal cats and dogs, while Houssay and Anderson [5] produced diabetes in cats and dogs subjected to subtotal pancreatectomy. De Bodo and his colleagues [6] showed that growth hormone decreased the exaggerated response to insulin of the dog subjected to hypophysectomy and, on continued administration, completely abolished this animal's insulin hypersensitivity. Concomitantly, growth hormone caused in these dogs impairment in the glucose tolerance indicative of diabetes mellitus and also produced an insulin resistance even to large doses of insulin.

In these experimental studies, growth hormone produced diabetes in every case. It is possible that this diabetogenic action of growth hormone represents an exaggeration of a truly physiological blood sugar-raising or anti-insulin action of the hormone in normal carbohydrate metabolism; however, evidence was lacking as to whether the normal animal's own growth hormone, under physiological conditions, antagonizes the action of insulin. It would appear necessary to present such evidence, since no conclusions with regard to the true physiological role of growth hormone can be drawn solely from its diabetogenic action. Reporting at the recent Laurentian Hormone Conference, de Bodo and Sinkoff [7] compared the insulin sensitivity of the dog subjected to adrenalectomy with that of the dog that had undergone hypophysectomy. They showed that the dog from which the adrenals had been removed, in the total absence of the adrenocortical steroids and epinephrine, was still far less sensitive to insulin than the dog in which hypophysectomy had been performed, which still secreted epinephrine and some adrenocortical steroids.[8] They concluded that this difference in insulin sensitivity was due to the presence of a functioning anterior pituitary gland in the dog subjected to adrenalectomy. The anterior pituitary factor responsible obviously was not corticotropin; also, it was known that the effects of the lactogenic, thyrotropic, and gonadotropic hormones in modifying insulin sensitivity were minimal. In view of previous work, these authors considered that this action was most probably due to growth hormone. Recently, Raben and Westermeyer reported [8a] that their growth hormone preparation was nitrogen-retaining and had little, if any, diabetogenic activity. Other investigators (Reid, Young, Li), as reported in discussions at the recent Laurentian Hormone Conference, have not corroborated these claims; rather, they stated that there is a strong parallel-

1. Houssay, B. A.: Carbohydrate Metabolism (Dunham Lecture), New England J. Med. **214**: 971 (May 14) 1936.

2. Richardson, K. C., and Young, F. G.: Histology of Diabetes Induced in Dogs by Injection of Anterior-Pituitary Extracts, Lancet **1**: 1098 (May 14) 1938.

3. Cotes, P. M.; Reid, E., and Young, F. G.: Diabetogenic Action of Pure Anterior Pituitary Growth Hormone, Nature, London **164**: 209 (Aug. 6) 1949.

4. Campbell, J.; Davidson, I. W. F.; Snair, W. D., and Lei, H. P.: Diabetogenic Effect of Purified Growth Hormone, Endocrinology **46**: 273 (March) 1950.

5. Houssay, B. A., and Anderson, E.: Diabetogenic Action of Purified Anterior Pituitary Hormones, Endocrinology **45**: 627 (Dec.) 1949.

6. de Bodo, R. C.; Kurtz, M.; Ancowitz, A., and Kiang, S. P.: Loss of Insulin Hypersensitivity and Development of Diabetes in Hypophysectomized Dogs Produced by Purified Growth Hormone, Proc. Soc. Exper. Biol. & Med. **74**: 524 (July) 1950; Anti-Insulin and Diabetogenic Actions of Purified Anterior Pituitary Growth Hormone, Am. J. Physiol. **163**: 310 (Nov.) 1950.

7. de Bodo, R. C., and Sinkoff, M. W.: Anterior Pituitary and Adrenal Hormones in the Regulation of Carbohydrate Metabolism, in Recent Progress in Hormone Research, New York Academic Press, Inc., to be published.

8. de Bodo, R. C.; Sinkoff, M. W., and Kiang, S. P.: Comparison of Insulin Hypersensitivity of Adrenalectomized and of Hypophysectomized Dogs, Proc. Soc. Exper. Biol. & Med. **80**: 350 (June) 1952.

8a. Raben, M. S., and Westermeyer, V. W.: Differentiation of Growth Hormone from the Pituitary Factor Which Produces Diabetes, Proc. Soc. Exper. Biol. & Med. **80**: 83 (May) 1952.

ism between the nitrogen-retaining and diabetogenic actions of growth hormone. Regardless of whether it is the growth hormone or some other anterior pituitary factor that is responsible for these actions in carbohydrate metabolism, the fact remains that some anterior pituitary factor, other than corticotropin, has an important role in the regulation of normal carbohydrate metabolism.

The evidence of physiological activity reported by de Bodo and associates,[8] although convincing, was still indirect. Therefore, it was deemed necessary to demonstrate an anti-insulin action of administered growth hormone in the dog subjected to hypophysectomy without the concomitant production of diabetes. If this effect could be achieved with the proper dosages under proper conditions, and continued indefinitely, it would be a demonstration of a truly physiological action of growth hormone in carbohydrate metabolism.

De Bodo and Sinkoff,[7] giving growth hormone intramuscularly in as small a dose as 0.02 mg. per kilogram of body weight a day, were able to partially reduce the insulin hypersensitivity of dogs that had undergone hypophysectomy, but, in some animals, even with these minimal doses, a concurrent tendency toward diabetes was noted. However, when a potent growth hormone preparation was given in combination with the adrenocortical steroids to these dogs, they were able to employ large doses for long periods of time without producing diabetes, insulin resistance, or toxic effects—all of which had been previously noted during growth hormone regimens alone. Moreover, the deranged carbohydrate metabolism of these dogs apparently was restored to normal.[7] This was of special interest, inasmuch as either the adrenocortical steroids or growth hormone used alone can produce diabetes if given in sufficiently large dosages. Thus growth hormone is a physiological blood sugar-raising agent that antagonizes the action of insulin, with its effectiveness dependent on hormonal balance with the adrenocortical steroids.

As to the mechanism of action of growth hormone in carbohydrate metabolism, it would seem that growth hormone does not enhance the new formation of sugar. Indeed, through its nitrogen-retaining action, it diminishes the gluconeogenesis from protein. Furthermore, it has not been shown that growth hormone facilitates glycogenolysis. Thus, examination of the diabetic glucose tolerance produced by this hormone indicates that the action of growth hormone is to inhibit the peripheral utilization of carbohydrate. Several groups of workers (Stadie and his associates [9] and Park and Daughaday [10]), working with isolated diaphragms from rats subjected to hypophysectomy and treated with growth hormone, demonstrated in vitro a decreased glucose uptake of the diaphragms of these rats as compared with the glucose uptake of diaphragms from untreated rats that had also undergone hypophysectomy. These in vitro findings are compatible with the observed effects of growth hormone in the living animal.

SYPHILIS AS AN OCCUPATIONAL HAZARD TO PHYSICIANS

Although accidentally acquired syphilis should be uncommon in physicians, a recent survey conducted by Epstein [1] suggests that it would be a mistake to ignore the possibility of innocently acquiring syphilis from patients. A total of 51 cases of extragenital chancres in physicians were reported by 32 of 125 dermatologists who answered questionnaires. In 35 instances the syphilitic lesions occurred on the fingers, in 6 instances in the nasal cavity, in 1 on an eyelid, and in 1 on an arm. Otolaryngologists were more frequently affected than any other well-defined group, and in six of them lesions developed. In addition, six cases of accidentally acquired syphilis were observed in interns, residents, and medical students; five cases occurred in general practitioners; and two were detected in pathologists. Routine clinical examination of patients produced infection in seven physicians, while in five physicians syphilis was acquired during obstetric procedures or during pelvic examination of patients. Three cases were attributed to tonsillectomy, three cases to wounds produced by needle puncture, and two cases were presumably due to exposure during surgical performance.

Stokes [2] and his associates assert that chancre of the finger and hand deserves special mention because early diagnosis of this lesion in physicians is all but unknown, owing to the infrequency with which it is suspected. In this connection, Fournier [3] declares that, of a group of 49 chancres of the hand coming under his supervision, 30 were in physicians; here, the syphilitic infection was attributed to manipulations of the genitalia during clinical examination and during operative procedures, to digital exploration of the oral cavity, and to tonsillectomy performed with bare hands. Moreover, Shaw [4] points out that one of the hazards connected with clinical and experimental studies on syphilis is the possible accidental inoculation of the investigator with Treponema pallidum. A physician who treats syphilitic patients or who handles syphilitic animals is liable to be inadvertently stuck, scratched, bitten, or otherwise contaminated with spirochetes. The medical literature describes a number of accidents with organisms obtained from both human and animal sources.

Fortunately, the incidence of medically acquired syphilis in physicians is low, owing to the decreased incidence of the disease, the use of rubber gloves, and to the

9. Stadie, W. C.; Haugaard, N.; Hills, A. G., and Marsh, J. B.: Hormonal Influences on Chemical Combination of Insulin with Rat Muscle (Diaphragm), Am. J. M. Sc. **218**: 265 (Sept.) 1949.

10. Park, C. R., and Daughaday, W. H.: Effect of Growth Hormone on Glucose Uptake and Glycogen Synthesis by Rat Diaphragm, Federation Proc. **9**: 212 (March) 1950.

1. Epstein, E.: Extragenital Syphilis in Physicians, California Med. **77**: 149 (Aug.) 1952.

2. Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: Modern Clinical Syphilology: Diagnosis, Treatment, Case Study, ed. 3, Philadelphia, W. B. Saunders Co., 1944.

3. Fournier, cited by Stokes.[2]

4. Shaw, C.: Accidental Inoculation with Spirochaeta Pallida, Arch. Dermat. & Syph. **44**: 878 (Nov.) 1941.

widespread adoption of aseptic techniques. Nevertheless, Epstein's report of 51 cases of extragenital primary syphilitic lesions in physicians indicates that syphilis constitutes a definite occupational hazard in the medical world.

CARCINOGENESIS AND THE PITUITARY GLAND

The frequent appearance of neoplasms in rats following prolonged administration of pituitary growth hormone [1] has led Moon and his associates to investigate the possible significance of pituitary function in neoplastic disease. In their initial experiments [2] the University of California workers gave 15 adult female rats intraperitoneal injections of pure pituitary growth hormone six days a week for approximately one year. Fifteen rats treated with human serum albumin served as controls. At autopsy, lymphosarcomas were present in the lungs of six of the animals receiving pituitary growth hormone. These neoplasms apparently arose from the peribronchial lymphoid tissue, which was hyperplastic in all 15 experimental animals. The adrenal medullas were also hyperplastic in all animals receiving hormone injections, and in 9 animals there were nodular areas of atypical medullary cells, interpreted as early neoplastic lesions, which in some instances had invaded the adrenal cortex. In six of the animals, the ovaries contained small atypical follicles that were considered as possibly being early stages of solid tumors. Such tumors were present in two animals, while in eight fibroadenomas were present in the mammary tissue.

In the control animals, no lymphosarcomas of the lung were observed, though in one animal adenomatosis was present; in a second, a stem-cell sarcoma was present in a mesenteric lymph node. No neoplasms of the adrenal glands were noted in the control animals, and the adrenal medulla appeared normal, while the appearance of the ovaries was consistent with the age of the animals. Only three of the control animals had fibroadenomas of the mammary tissue, and two of these were subsequently shown to have pituitary tumors. Examination of the pituitary glands of 11 experimental and 15 control animals revealed that in all of the former the acidophils were diminished in size and degranulated, while the chromophobes were increased in number. Adenomatous lesions, frequently found in old rats, were present in eight control and in all experimental animals that were studied.

In a second series of experiments,[3] 15 adult rats that had undergone hypophysectomy were treated with pituitary growth hormone and 15 received human serum albumin. In three of the experimental animals there was hyperplasia of the peribronchial lymphoid tissue, but no pulmonary lymphosarcomas were observed. No tumors of the medulla were noted, and the adrenal cortexes showed only atrophy typical of hypophysectomy. One tumor of the ovary was present in the experimental group and one in the control animals. These were the only neoplasms occurring in either the experimental rats or the controls.

The demonstration that the diverse neoplasms that develop in normal animals treated with pituitary growth hormone do not arise in similarly treated animals that have undergone hypophysectomy led to a study of the effect of hypophysectomy on methylcholanthrene carcinogenesis. In a recently reported study,[4] it was noted that in 8 of 15 normal animals implanted with methylcholanthrene rapidly growing tumors developed, while in four others a palpable increase of connective tissues developed at the site of implantation. Of 15 rats subjected to hypophysectomy and treated with methylcholanthrene, in only one did sarcoma develop at the site of implantation, and there was little or no local reaction to implantation in the others. These preliminary studies, which indicate that the presence of the pituitary gland is necessary for the production of neoplasms following the administration of both pituitary growth hormone and the chemical carcinogen methylcholanthrene, will doubtless stimulate further investigation in this interesting and important field.

YOLK SAC DIAGNOSIS OF TUBERCULOSIS

Several investigators have demonstrated that Mycobacterium tuberculosis multiplies with great rapidity in the yolk sac of embryonated eggs. Making use of this rapid multiplication, Brueck and Buddingh [1] of the department of microbiology of Louisiana State University, devised a technique for the isolation of tubercle bacilli in clinical material that is apparently free from acid-fast bacilli by routine microscopic tests. In a typical experiment, six embryos that had been incubated for five to eight days were each inoculated in the yolk sac with 0.2 to 0.5 cc. of clinical material that was apparently free of tubercle bacilli and to which penicillin or chloramphenicol was usually added. Numerous acid-fast bacteria were demonstrated by the fourth to sixth day in the yolk material, and these were afterward fully identified by guinea pig tests.

Thus far, 50 clinical specimens apparently containing no tubercle bacilli have been examined by the yolk sac technique with positive results in 39. The specimens included spinal fluid, sputum, gastric washings, and pleural, peritoneal, and pericardial fluids. The new technique may well prove to be a useful addition to current diagnostic methods.

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2. Moon, H. D.; Simpson, M. E.; Li, C. H., and Evans, H. M.: Neoplasms in Rats Treated with Pituitary Growth Hormone: I. Pulmonary and Lymphatic Tissues, Cancer Res. **10**: 297-308, 1950; Neoplasms in Rats Treated With Pituitary Growth Hormone: II. Adrenal Glands, ibid. **10**: 364-370, 1950; Neoplasms in Rats Treated With Pituitary Growth Hormone: III. Reproductive Organs, ibid. **10**: 549-556, 1950. Koneff, A. A., and others: Neoplasms in Rats Treated With Pituitary Growth Hormone: IV. Pituitary Gland, ibid. **11**: 113-117, 1951.

3. Moon, H. D.; Simpson, M. E.; Li, C. H., and Evans, H. M.: Neoplasms in Rats Treated with Pituitary Growth Hormone: VI. Absence of Neoplasms in Hypophysectomized Rats, Cancer Res. **11**:535-539, 1951.

4. Moon, H. D.; Simpson, M. E., and Evans, H. M.: Inhibition of Methylcholanthrene Carcinogenesis by Hypophysectomy, Science **116**:313 (Sept. 26) 1952.

1. Brueck, J. W., and Buddingh, G. J.: Isolation of M. Tuberculosis by Inoculation of the Yolk Sac of Embryonated Eggs, Proc. Soc. Exper. Biol. & Med. **80**: 589 (Aug.-Sept.) 1952.

MEDICAL NEWS

CALIFORNIA

Dr. Chandler Resigns as Dean.—Dr. Loren R. Chandler, since 1933 dean of Stanford University School of Medicine, San Francisco, has resigned effective on selection of a new dean. Dr. Chandler wishes to devote full time to surgical research problems, particularly those associated with diseases of the pancreas, liver, and spleen in children. He will remain as a full-time professor of surgery. In 1941-1942 Dr. Chandler served as president of the Association of American Medical Colleges and in 1942 as president of the California Academy of Medicine. As a member of a three man committee appointed by the American Medical Association, Dr. Chandler was in England two years ago to study medical schools and research and the effects of the British National Health Service Act.

COLORADO

Colorado's Aging Population.—A report on Colorado's aging population and some chronic illness problems, recently prepared by the Colorado State Department of Public Health, discloses the following facts: 1. From 1900 to 1950, the group aged 65 years and older has multiplied nearly 8½ times, while the general population has multiplied only 2½ times. 2. In 1950, 8.7% of the population was 65 and older, in comparison with 2.6% in 1900. 3. Of the total deaths among Colorado residents in 1950, 63% were attributable to two broad groupings of chronic diseases, the cardiovascular-renal diseases and cancer. Although more characteristic of the older ages, these diseases also took heavy tolls among younger groups, accounting for 26% of the deaths at ages 5-14; 19% at ages 15-24; 37% at ages 25-44; 68% at ages 45-64; and 78.2% among those 65 and older. The report, along with an extensive bibliography on these problems, is available to physicians on request to the Colorado State Department of Public Health.

GEORGIA

Society News.—At its annual meeting at Savannah, the Georgia Heart Association elected the following officers: president, Dr. Thomas L. Ross Jr., Macon; president-elect, Dr. Joseph C. Massee, Atlanta; vice-president, Dr. Clarence C. Butler, Columbus; and secretary, Dr. Herbert D. Tyler, Thomaston.

Medical School Opens Research Building.—The Woodruff Memorial Building, the 2 million dollar center for medical research, was recently opened at Emory University in Emory University, Ga. The seven story structure, connected by closed walkways with Emory University Hospital, was made possible by grants from private donors and from the National Cancer Institute.

ILLINOIS

Memorial Scholarship Fund.—In memory of his son, who was killed in Europe during World War II, Dr. Pliny R. Blodgett, Chicago Heights, has established a scholarship fund, from which scholarships in postgraduate lecture courses sponsored by the Illinois Academy of General Practice are to be awarded. Scholarships will be granted only to American citizens who are members of the Illinois Academy of General Practice. If the qualifications are equal, preference will be given to those persons who have served in the armed forces and to the sons and daughters of veterans, provided that physicians educated at government expense under the Army Special Training Program or V-12 Program, and who have not subsequently served in the armed forces, shall not be eligible for an award. No one is to be considered for any award who advocates the overthrow of the government of the United States or who advocates political control of medicine. Five awards for one course of postgraduate instruction will be provided annually. Recipients of awards, when financially able to do so, will be expected to repay to the fund an amount at least equal to that received. In the event that the Illinois Academy of General Practice discontinues its postgraduate courses of instruction, any money remaining in the fund will be paid to the American Medical Education Foundation fund to aid in the educational program at Dr. Blodgett's alma mater, the University of Illinois College of Medicine, Chicago.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education and public health. Programs should be received at least three weeks before the date of meeting.

Chicago

Society News.—The 1952-1953 officers of the Chicago Society of Industrial Medicine and Surgery are as follows: Dr. George W. Bohr, president; Dr. Will F. Lyon, vice-president; and Dr. Charles M. Drueck, secretary-treasurer.

Hospital News.—Passavant Memorial Hospital recently announced that gifts of $625,000 had been received as advance donations toward the hospital's 3 million dollar building program. The funds will be used to build a 10 story pavilion on the south end of the hospital building and to remodel the present structure, which was constructed in 1928. The program will add 100 beds to the hospital's 265 bed capacity.

Dr. Max Cutler Moves to California.—Dr. Max Cutler has moved to Los Angeles, where he will engage in private practice in the field of clinical cancer. He will return to Chicago periodically to help the Chicago Tumor Institute with its clinical and research program. Dr. Cutler came to Chicago from New York in 1931 to found the Michael Reese Tumor Clinic, which he directed until 1937, when he became visiting professor of surgery in the Peking Union Medical College, in China, under the auspices of the China Medical Board of the Rockefeller Foundation. Dr. Cutler and the late Dr. Ludvig Hektoen in 1938 founded the Chicago Tumor Institute, and he is now president of the board. For 15 years he was director of cancer research of the Veterans Administration and cancer consultant to the Veterans Administration Hospital, Hines, Ill.

Personal.—Dr. Karl A. Meyer, chairman of research in poliomyelitis and cancer being conducted by the Dr. Jerome D. Solomon Memorial Research Foundation at Hektoen Institute, recently received the foundation's "Heart of Gold" award.——Dr. Francis J. Gerty, director, Psychiatric Division, Illinois Neuropsychiatric Institute, has been appointed a member of the National Advisory Mental Health Council of the U. S. Public Health Service, Washington, D. C.——At a recent meeting of the Illinois Division of the American Cancer Society, Dr. Herbert E. Schmitz received an award for outstanding service in cancer control.——Dr. Jack D. Kirshbaum, director of laboratories of the San Bernardino County Hospital, San Bernardino, Calif., has been appointed associate professor in the department of pathology at the College of Medical Evangelists, Loma Linda, Calif. Dr. Kirshbaum was formerly acting head of the department of pathology, Chicago Medical School, and attending pathologist at the Cook County Hospital, Chicago.——Dr. Lester R. Dragstedt, professor of surgery, University of Chicago School of Medicine, gave the fifth annual Phi Delta Epsilon lectureship at the University of Toronto Faculty of Medicine, Ontario, Canada, Nov. 17, on "Physiology of Gastric Secretion and the Peptic Ulcer Problem."——Capt. Emil J. Stein, U. S. Navy, retired, has been named night warden of Cook County Hospital. Dr. Stein has been engaged in research and postgraduate work in surgery since 1950 at Cook County Graduate School of Medicine.——Dr. Paul C. Bucy, professor of neurology and neurological surgery at the University of Illinois College of Medicine, will be the first surgeon to occupy the George A. Ball

visiting professorship in surgery at Indiana University School of Medicine, Indianapolis. The new chair in surgery was established by the Riley Memorial Association in honor of the philanthropist for whom it is named.

KANSAS

Fluoridation of Water Supply.—Hays, El Dorado, Coffeyville, and Minneapolis are the most recent cities to make the fluoride adjustment of their public water supplies for the partial control of dental decay in children's teeth. Ten Kansas communities now have made the fluoride adjustment at an annual per capita cost ranging from 5 to 14 cents, variation in cost depending on the local waterworks set-up, the compound used, and the amount of fluoride already present in the water.

Course in Environmental Sanitation.—The Topeka Field Training Center announces an eight week field training course in environmental sanitation, Jan. 12 to March 7, 1953, at the new quarters of the center in the Medical Society Building, 315 W. Fourth St. The course is designed to supplement academic training in specialized subjects of environmental health and to provide for internship training for new employees by the use of practical assignments in regular activities of an operating health department. Classroom instruction and laboratory and field exercises will be given. Applications should be made through the Kansas State Board of Health, Topeka.

KENTUCKY

State Society Telephone Seminars.—Lantern slides, together with a manual and other visual aids, will be sent to subscribing county societies for the Kentucky State Medical Association's 1953 telephone seminars (Jan. 27, Feb. 24, March 31, and April 28). The slides, which will be flashed on screens in county society meeting rooms, will be discussed by the panel.

Personal.—Gov. Lawrence W. Wetherby has appointed Dr. Thomas P. Leonard, Frankfort, a member of the state board of health, to fill the vacancy created by the death of Dr. Finis M. Travis, Frankfort.——At the general public meeting, held in connection with the annual convention of the Kentucky State Medical Association in Louisville, the distinguished service medal was presented to Dr. John W. Scott, Lexington, president of the association in 1939 and 1940, and the J. Watts Stovall award, for the most outstanding general practitioner, to Dr. Charles L. Sherman, Millwood.

MICHIGAN

Course in Cancer Detection.—Wayne University College of Medicine, Detroit, offers a graduate course in the early detection of cancer. The course may be taken for the entire year or for any quarter. The second quarter is from Dec. 8 to March 14, 1953, and the third quarter, March 16 to June 13, 1953. Registration can be made in the office of Postgraduate Medical Education, 1512 St. Antoine, Detroit 26. Tuition is $50 per quarter, and the class is limited to 15.

Dr. Towey Receives Dearholt Medal.—Dr. John W. Towey of Powers has been named the 1952 recipient of the Dearholt medal, bestowed by the Mississippi Valley Conference on Tuberculosis. The presentation sketched Dr. Towey's "inspirational career," during which, after winning his personal battle with tuberculosis, he became head of the Pinecrest Sanatorium when it opened 30 years ago, and through his determination, helped win tuberculosis prevention for the residents of the area.

MISSOURI

Dr. Dammin Goes to Harvard.—Dr. Gustave J. Dammin, chairman, pathology department, Washington University School of Medicine, St. Louis, has been appointed professor of pathology in the Harvard Medical School, Boston, succeeding Dr. Clinton Van Zandt Hawn, who has resigned for reasons of health. Dr. Dammin, who has been pathologist-in-chief of Barnes Hospital in St. Louis, will occupy a like position at Peter Bent Brigham Hospital in Boston. During World War II, he was in charge of the Army's Puerto Rican Department Laboratory; he received the Legion of Merit award for work as executive officer and parasitologist of the Dysentery Commission in the India-Burma Theatre. In 1945-1946, he was director of the Laboratories Division, Office of the Surgeon General, and since then has been a consultant to the Surgeon General. He also is adviser to the federal Civil Defense Administration.

NEW YORK

Dr. Trudeau Resigns Sanatorium Presidency.—Dr. Francis B. Trudeau, son of the founder of Trudeau Sanatorium at Saranac Lake, has retired as president of the sanatorium but will continue as trustee. Dr. J. Burns Amberson Jr., vice-president of the sanatorium, will become its president. Dr. Amberson, who is a former president of the American Trudeau Society and the New York Tuberculosis and Health Association, is visiting physician in charge of the Bellevue Hospital chest service and professor of medicine at the Columbia University College of Physicians and Surgeons.

Centennial Dinner.—At the 100th anniversary of Livingston County Medical Society, recently celebrated in Mount Morris, Dr. Edward T. Wentworth, president of the Medical Society of the State of New York, presented 50 year certificates to Drs. Judson M. Burt, Caledonia, George H. Dill, Lima, Francis V. Foster, Caledonia, and Willard H. Veeder, Geneseo. Dr. Samuel Sanes, Buffalo, president of the Erie County Medical Society, spoke on "Medical Aspects of Crime," and Dr. Samuel A. Munford of Clifton Springs, president of the state medical society's Seventh District Branch, outlined the importance of the county medical society in community activities and in the advancement of postgraduate scientific education. A history of the society, written by Dr. LeGrand A. Damon of Sonyea, was presented.

Academy Offers Prizes.—The Rochester Academy of Medicine has announced the following prize awards for 1953: 1. The Paine prize ($200, accompanied by a certificate of award, for the best thesis on any medical subject) will be awarded through the courtesy of the Paine Drug Company to a member of the academy not engaged in full-time research. 2. The Rochester Regional Hospital Council award ($100, accompanied by a certificate of award, for the best thesis on any medical subject) will be presented to a physician residing in the counties of Allegany, Chemung, Livingston, Monroe, Ontario, Orleans, Schuyler, Seneca, Steuben, Wayne, or Yates. 3. The 1953 Monroe pharmacy award in memory of Dr. David B. Jewett ($100, accompanied by a certificate of award) will be given for the best case report presented by any house officer of the staff of any hospital in Monroe County. The Rochester Regional Hospital Council also offers an award to nurses.

New York City

Dr. Dublin Retires.—Louis I. Dublin, Ph.D., second vice-president and statistician of the Metropolitan Life Insurance Company, having reached retirement age, will retire, in accordance with the company's plan, at the end of this year.

Health Centers Opened.—The New York City Department of Health has recently opened two enlarged health centers, one in the Jamaica health district and the other in the East Harlem district. Among the new services that will be provided in the East Harlem center are a cancer detection-prevention center, a tropical disease clinic, and a unit of the health department's bureau of nutrition.

Society News.—The Bronx Dermatological Society presented the following symposium on pigment tumors, Dec. 18, at the New York Academy of Medicine:

Melanin Formation in Man, Aaron B. Lerner and Thomas B. Fitzpatrick, Portland, Ore.
Current Status of the Clinicopathologic Correlation of Nevi and Malignant Melanomas, Arthur C. Allen and Sophie Spitz, New York.
Management of Pigmented Nevi, Samuel B. Frank, White Plains.

Drs. Marion B. Sulzberger, Samuel M. Peck, and Wilbert Sachs, New York, served as discussants.

NORTH CAROLINA

Collection of Medical Pictures.—Through a grant from the Doris Duke Foundation, the Duke University School of Medicine, Durham, has acquired a picture collection of famous physicians and medical scenes for the new Duke medical research building. The 250 framed steel engravings have been collected over a long period by Dr. J. Calvin Weaver of Atlanta, Ga., an authority on Georgia medical history. Duke Medical School Library also houses the library of the Georgia Medical Society, founded in 1804 at Savannah.

OHIO

Course in Forensic Medicine.—Western Reserve University School of Law in Cleveland will inaugurate a graduate program in forensic medicine, the first course, "Medical Aspects of Civil Litigation," meeting from 7 to 9 p. m. for 14 Monday evenings, beginning Feb. 2, 1953. The legal medicine program, as it expands, will provide courses for lawyers, physicians, social workers, and certain public officials. According to Prof. Oliver C. Schroeder Jr., associate professor of law, who will direct the program, the aim will be to acquaint these groups with the scientific medical evidence and the vital legal statutes and decisions needed for the best civil and criminal administration of justice. Facilities of the Institute of Pathology, Law School, Medical Center, and the Cuyahoga County coroner's laboratory and offices will be used. The faculty of the legal medicine course will include the following Cleveland physicians, all of whom are staff members at the School of Medicine and the Institute of Pathology: Lester Adelson, Alfred Bochner, Charles W. Elkins, Samuel R. Gerber, Edward O. Harper, Charles H. Herndon, Herbert H. Johnson Jr., Lorand V. Johnson, Roscoe D. Leas, Wilbert H. McGaw, Alan R. Moritz, George L. Sackett, and Rogert B. Scott.

PENNSYLVANIA

Society News.—At a recent meeting of the Reading Eye, Ear, Nose and Throat Society, Dr. Isadore Givner, New York, lectured on "Associated Eye and Skin Manifestations of Systemic Disease." Dr. Philip R. Wiest, Reading, served as moderator for a study club on external otitis. Instructors were Drs. Michael J. Penta, Reading, and C. Fremont Hall, Phoenixville.

Benjamin Rush Award.—The Erie County Medical Society has selected George Bach of Erie to receive the 1952 Benjamin Rush award for "his long record of unselfish service to his community, as a leader in its industry, culture, and social welfare." Mr. Bach has been active in the management of St. Vincent's Hospital, Erie, and in work with the Community Chest, Red Cross, Boy Scouts, mayor's committees, and Rotary.

Cancer Research Project.—The U. S. Public Health Service has authorized a grant of $47,334 to the University of Pennsylvania for a survey to determine whether men inherit cancer from cancer-afflicted women of their families. The survey will be confined to investigation of an estimated 5,000 male members of 400 family groups. Four trained women investigators will be engaged until 1955 in accumulating information. The survey will extend to many parts of the United States and other countries and will be directed by Dr. Douglas P. Murphy, assistant professor of obstetrics and gynecology. Three aspects of cancer will be stressed in the present investigation: (1) the possible role played by heredity in the etiology of cancer in general, (2) the possibility that the presence of cancer in the female members of a family increases the chance that the disease will affect the male members, and (3) the correlation between the frequency of cancer in one generation and its frequency in the following one.

Philadelphia

University News.—At Hahnemann Medical College and Hospital of Philadelphia, Dr. B. Marvin Hand, formerly assistant professor of neurology, has been promoted to professor of neurology, and Dr. Van B. Osler Hammett has been appointed professor of psychiatry.

Bequests and Donations.—Lankenau Hospital has been awarded the bulk of the $1,682,949 estate of Mrs. Louisa Elizabeth Nax. The income is to be used "for research work for the elimination and cure of cancer."——The University of Pennsylvania has been awarded $50,000 in an Orphans' Court adjudication of the estate of Dr. James M. Anders, who died Aug. 29, 1936. The bequest, to be known as the James M. Anders Foundation, is to be added to the endowment fund of the Medico-Chirurgical College and the Hospital of the Graduate School of Medicine. ——Jefferson Medical College and Hospital have received a grant of $552,000 from the Anthracite Health and Welfare Fund for the continuance of research and treatment of silicosis. The grant, to cover a period of four years, follows an earlier grant of $575,000.

SOUTH CAROLINA

Outbreaks of Infectious Hepatitis.—Dr. Benjamin F. Wyman, South Carolina State Board of Health, Columbia, reports outbreaks of infectious hepatitis in two universities. In one school since the middle of October, 165 cases have been diagnosed clinically. Sporadic cases have also occurred in the city where the school is located. Ten cases have been reported in another university since the beginning of the current school year.

TEXAS

Human Rabies.—Simon E. Sulkin, Ph.D., Southwestern Medical School of the University of Texas, Dallas, has recovered rabies virus from the brain of a 9-year-old child who was dead on arrival at the hospital. This was the third case of human rabies in that area within seven months and the sixth reported in Texas this year.

Society News.—At its annual meeting in Dallas the Texas Pediatric Society named Dr. Joseph A. Bybee, Beaumont, president; Dr. Robert L. Moore, Dallas, president-elect; Dr. Margil C. Carlisle, Waco, secretary; Dr. James N. Walker, Fort Worth, secretary-elect; and Dr. Jack M. Woodall, Big Springs, treasurer. ——The *Texas State Journal of Medicine* has moved its headquarters to 1801 Lamar Blvd., Austin.

UTAH

Fellowship in Pediatric Cardiology.—Applications are being accepted for a fellowship in pediatric cardiology, to begin in July, 1953, at the University of Utah School of Medicine, Salt Lake City. Applicants may write to Dr. Hans H. Hecht, associate professor of medicine, University of Utah School of Medicine, University St., Salt Lake City.

Personal. — Dr. John C. Nunemaker, chief of medical service, Veterans Administration Hospital, Salt Lake City, has been assigned chief of research in the division of medicine and surgery, Veterans Administration, Washington, D. C.——Dr. James Z. Davis, Salt Lake City health commissioner and chairman, state board of health, has been awarded a certificate of merit by the Prudential Insurance Company for "pioneering in the work of furthering child safety in Salt Lake City."

WISCONSIN

Neurology and Psychiatry in General Practice.—The University of Wisconsin Medical School, Madison, offers a course in neurology and psychiatry for general practitioners Jan. 6-8, 1953, under the direction of Dr. William J. Bleckwenn, professor of neuropsychiatry. Enrollment will be limited to 40 applicants. Application for registration should be sent in advance to Dr. Robert C. Parkin, co-ordinator of Graduate Medical Education, University of Wisconsin Medical School, 418 N. Randall Ave., Madison 6. Course fee, $20.

Personal.—Dr. Hugh P. Conway was recently honored by citizens of the Spring Valley area at a testimonial dinner and program given in recognition of his 50 years of service as a general practitioner in Spring Valley.——Dr. Harry D. Bouman, professor of physical medicine, University of Wisconsin Medical School, Madison, has been elected editor of the *American Journal of Physical Medicine,* succeeding Dr. Sidney Licht of Bos-

ton University School of Medicine and Tufts College Medical School, who resigned after five years of service. The magazine changed its name from *Occupational Therapy and Rehabilitation* to the present title.——Dr. Willard A. Pease, Rio, was recently honored when the community celebrated his 50 years of service with a reception in the Rio High School. Dr. James MacGregor, Portage, was toastmaster, and Dr. Charles W. Henney, Portage, was the main speaker at the program.——Dr. Glenn F. Treadwell of Friendship was recently the honored guest at a testimonial program at the Adams County Fairgrounds. In appreciation of his 40 years of service, Dr. Treadwell was presented with a gold watch and a gift of money, and Mrs. Treadwell was given a radio.——Dr. Edwin C. Welsh, clinical instructor in physical medicine and rehabilitation at Marquette University School of Medicine, Milwaukee, has been appointed director of Columbia Hospital's department of physical medicine and rehabilitation. He will continue his work at the university as well as at the Veterans Administration Center, Wood, where he has served as assistant chief in his specialty.

GENERAL

New Bimonthly Journal.—The Histochemical Society announces that in January, 1953, it will begin publication of the *Journal of Histochemistry and Cytological Chemistry*, a bimonthly periodical, which will be edited by Dr. Ralph D. Lillie of the National Institutes of Health, Bethesda, Md. Subscription price, $7.50.

Essay Contest.—The Mississippi Valley Medical Society offers a cash prize of $100, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest and practical value to general practitioners. Contestants must be members of the American Medical Association and citizens of the United States. Contributions must be typewritten in English, submitted in five copies, not exceeding 5,000 words, and must be received not later than May 1, 1953. Other details may be secured from Dr. Harold Swanberg, Secretary, Mississippi Valley Medical Society, 209-224 W.C.U. Bldg., Quincy, Ill.

Outbreaks of Gastroenteritis.—The Kentucky State Department of Health reports an outbreak of gastroenteritis among 300 high school students, 63 of whom became ill from 4 to 29 hours after eating the lunch at the school. An unopened bottle of pasteurized milk, obtained from the school supply, revealed hemolytic Staphylococcus aureus.——The Washington State Department of Health reports an outbreak of gastroenteritis among 300 persons who attended a church supper. About 120 persons became ill after ingestion of the meal. Laboratory examination revealed a nonhemolytic gram-positive micrococcus in a specimen of chicken.

Meeting of Otolaryngologists.—The Eastern Section meeting of the American Rhinological, Laryngological and Otological Society will begin at 9:30 a. m., Jan. 7, 1953, in the Syracuse Hotel, Syracuse, N. Y. The following papers will be presented:

Fact and Fallacies of Bone Conduction, Francis L. Weille, Boston.
Bronchologic Aid in Bronchopulmonary Diagnosis, Louis H. Clerf, Philadelphia.
Endaural Modified Radical Mastoidectomy, James A. Moore, New York.
Advances in the Use of Antibacterial Substances, Paul A. Bunn, Syracuse, N. Y.
Therapeutic Management of Certain Endological Problems, Herrmann E. Bozer, Buffalo.
Biostatistical Studies in Otolaryngology, Orren D. Chapman, Syracuse, N. Y.

Poliomyelitis Fellowships.—The National Foundation for Infantile Paralysis announces the availability of a number of additional postdoctoral fellowships to candidates whose interests are research and teaching in medicine and the related biological and physical sciences. The purpose of these fellowships is to increase the number of professional workers qualified to give leadership in the solution of basic and clinical research problems of poliomyelitis and other crippling diseases. The fellowships, which cover from one to five years, carry stipends ranging from $3,600 to $7,000 a year. Institutions that accept fellows receive additional compensation for expenses incurred in relation to their training programs. Eligibility requirements include United States citizenship, sound health, and a master's, doctor's, or equivalent degree. Information may be obtained from: Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5.

Aid in Returning Cardiac Patients to Work.—Three booklets on the employment of cardiac patients are being distributed by the American Heart Association to assist private and industrial physicians in restoring such patients to gainful employment. "Returning Cardiacs to Work," written by the Bellevue Hospital Work Classification Unit, is intended to help physicians evaluate the physical capacity and occupational possibilities of cardiac patients. This manual includes a list of official, voluntary, and private agencies to which the physician may refer patients for vocational counseling or retraining. "Facts About Employment and Heart Disease," written in question-and-answer form by Dr. Leonard Goldwater, New York, is aimed directly at the cardiac worker. "These Hands Are Able" was developed from a manuscript prepared by the Cardiacs in Industry Committee of the Los Angeles County Heart Association. All three booklets may be obtained through heart association affiliates or from the American Heart Association, 44 E. 23rd St., New York 10.

Symposium on Tuberculosis.—The American Association for the Advancement of Science will hold its 119th meeting Dec. 26-31 in Kiel Auditorium, St. Louis. Saturday at 2 p. m. the following symposium on "Chemotherapy of Tuberculosis" will be presented in Assembly Hall 3:

Antimicrobial Therapy of Pulmonary Tuberculosis, Forrest W. Pitts, Captain (MC), U. S. Army, and Carl W. Tempel, Colonel (MC), U. S. Army, Denver.
Laboratory Evaluation of the Antitubercular Activity of the Hydrazine Derivatives of Isonicotinic Acid, Emanuel Grunberg, Ph.D., Nutley, N. J.
Pharmacology of the INAH Compounds, Carl C. Pfeiffer, Chicago.
Use of Isoniazid and Iproniazid Compounds in Tuberculosis, Meyer R. Lichtenstein, Chicago.

On Sunday at 2 p. m. a conference will be held on problems that confront those persons who prepare scientific manuscripts and who are concerned with the preparation of technical reports. The Oak Ridge (Tenn.) Institute for Nuclear Studies will hold its meeting on Monday in Room 4C. Five papers on "Nuclear Science and Industry" will be presented in the morning and four papers on "Research Applications of Carbon-14" in the afternoon.

Society News.—At its St. Louis meeting the Mississippi Valley Medical Society installed Dr. John I. Marker of Davenport as president; named Dr. Norris J. Heckel, Chicago, president-elect, and Drs. James S. Jackson, Mount Pleasant, Ia., David A. Bennett, Canton, Ill., and Arthur W. Neilson, St. Louis, vice-presidents; and reelected Dr. Harold Swanberg, Quincy, Ill., secretary-treasurer.——The American Society of Anesthesiologists has installed Dr. Ralph T. Knight, Minneapolis, as president and named Dr. Stevens J. Martin, Hartford, Conn., president-elect; Dr. Brant B. Sankey, Cleveland, first vice-president; Dr. Irving M. Pallin, Brooklyn, second vice-president; Dr. J. Earl Remlinger, Evanston, Ill., secretary; and Dr. Moses H. Krakow, New York, treasurer.——The Neurosurgical Society of America has elected the following officers: Dr. William F. Meacham, Nashville, Tenn., president; Drs. Kenneth E. Livingston, Portland, Ore., and Harry P. Maxwell, Milwaukee, vice-presidents; Dr. I. Joshua Speigel, Chicago, treasurer; and Dr. Clarence D. Hawkes, Memphis, Tenn., secretary. The next annual meeting will be held at the Broadmoor, Colorado Springs, Colo., Sept. 23-27, 1953.

Congress on Medical Librarianship.—A group of British medical librarians has begun preparations for the First International Congress on Medical Librarianship in London during the week of July 20, 1953. Sir Cecil Wakeley, president of the Royal College of Surgeons, has accepted the honorary chairmanship of the congress; the planning committee includes Mr. W. J. Bishop, librarian, Wellcome Historical Library; Mr. W. R. LeFanu, librarian, Royal College of Surgeons; and Mr. F. N. L. Poynter. Among the honorary vice-presidents appointed are: Mr. James F. Ballard and Dr. Henry R. Viets of the Boston Medical Library; Dr. John F. Fulton of Yale University, New Haven, Conn.; Dr. Sanford V. Larkey, librarian, Welch Medical Library; Mr. Wil-

liam D. Postell, librarian, Louisiana State University School of Medicine; Miss L. Margueriete Prime, librarian, American College of Surgeons; and Lieut. Col. Frank B. Rogers, director, Armed Forces Medical Library, Washington, D. C. The Medical Library Association, at its recent meeting in Lake Placid, voted to make a cash contribution to this international congress. Information can be obtained by writing to Mr. Bishop in London or to Miss L. Margueriete Prime, American College of Surgeons, 40 E. Erie St., Chicago 11.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories, and possessions in the weeks ended as indicated:

Area	Nov. 29, 1952	Nov. 22, 1952	Dec. 1, 1951
New England States			
Maine	5	1	..
New Hampshire	..	1	..
Vermont	1	2	1
Massachusetts	5	6	1
Rhode Island	..	2	..
Connecticut	3	3	..
Middle Atlantic States			
New York	41	46	19
New Jersey	8	10	2
Pennsylvania	12	26	14
East North Central States			
Ohio	24	21	13
Indiana	8	17	1
Illinois	23	45	16
Michigan	38	52	10
Wisconsin	12	28	10
West North Central States			
Minnesota	35	55	15
Iowa	11	30	..
Missouri	8	10	10
North Dakota	5	8	3
South Dakota	14	27	1
Nebraska	19	37	3
Kansas	8	16	10
South Atlantic States			
Delaware	1	1	..
Maryland	1	2	3
District of Columbia	3	1	..
Virginia	2	8	2
West Virginia	5	9	5
North Carolina	6	10	1
South Carolina	..	..	..
Georgia	3	11	9
Florida	12	23	4
East South Central States			
Kentucky	22	11	8
Tennessee	8	10	5
Alabama	6	3	5
Mississippi	2	..	13
West South Central States			
Arkansas	2	1	10
Louisiana	4	6	8
Oklahoma	4	9	11
Texas	9	14	46
Mountain States			
Montana	1	10	7
Idaho	4	5	..
Wyoming	2	1	3
Colorado	8	16	13
New Mexico	8	6	..
Arizona	6	10	..
Utah	16	7	15
Nevada	5	4	1
Pacific States			
Washington	22	28	16
Oregon	6	4	12
California	174	180	101
Territories and Possessions			
Alaska	3	9	..
Hawaii	6	1	..
Puerto Rico	..	..	2
Total	631	843	429

FOREIGN

Prize for Medicosurgical Film.—*La Presse Médicale* announced that its annual prize of 100,000 French francs (approximately $290) for a medicosurgical film and various other awards will be given during the last session of the course in current medicosurgical questions at the Faculté de Médecine de Paris, March 24, 1953. The award is available only for unpublished, amateur films that have not been subsidized or produced by any laboratory or firm. Sound films or silent, black-and-white or colored films may be submitted but must be of 16 mm. size and must be received by March 10, 1953. Entries may be sent to the secretary, *La Presse Médicale*, 120 Boulevard St. Germain, Paris, France.

LATIN AMERICA

Congress of Military Medicine and Pharmacy.—The 14th International Congress of Military Medicine and Pharmacy, which was scheduled to be held in Montevideo, Uruguay, March 1-7, 1953 (*J. A. M. A.* **150:**1322 [Nov. 29] 1952) will not be held in that city. The location of the meeting will be announced later.

CORRECTION

Radioactive Iodine in Treatment of Hyperthyroidism.—In the article entitled "Five Year Experience with Radioactive Iodine in Treatment of Hyperthyroidism" in THE JOURNAL, Nov. 29, 1952, the first sentence in the last paragraph on page 1269 should read "At the present time a dose of 150 μc [microcuries]. . . ." The same applies to the remainder of the paragraph at the top of page 1270, which should read "250 μc" and "300-350 μc."

EXAMINATIONS AND LICENSURE

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 23-25. Sec., Dr. D. G. Gill, 537 Dexter Ave., Montgomery.

ALASKA:* *Examination.* Juneau, March 3. On application in other towns where there are board members. *Reciprocity.* On application. Sec., Dr. W. M. Whitehead, Box 140, Juneau.

ARKANSAS:* *Homeopathic. Examination.* Little Rock, April 6. Sec., Dr. Carl S. Bungart, 105 North 14th St., Ft. Smith.

COLORADO:* *Examination.* Denver, Jan. 13-16. Exec. Sec., Mrs. B. H. Hudgens, 831 Republic Bldg., Denver.

CONNECTICUT:* *Homeopathic.* Derby, March 10-11. Sec., Dr. Donald A. Davis, 38 Elizabeth St., Derby.

DELAWARE: *Examination.* Dover, Jan. 13-15. *Reciprocity.* Dover, Jan. 22. Sec., Dr. J. S. McDaniel, 229 South State St., Dover.

GEORGIA: *Examination.* Atlanta and Augusta, June. *Reciprocity.* Atlanta, June. Sec., Mr. R. C. Coleman, 111 State Capitol, Atlanta.

GUAM: The Commission on Licensure will meet whenever a candidate appears or submits his credentials. Ex. Sec., Dr. Austin W. Matthis, Agana.

HAWAII: Honolulu, Jan. 12-14. Sec., Dr. I. L. Tilden, 1020 Kapiolani St., Honolulu.

IDAHO: Boise, Jan. 12-14. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

ILLINOIS: Chicago, Jan. 27-29. Supt. of Regis., Mr. Charles F. Kervin, Capitol Bldg., Springfield.

INDIANA: *Examination.* Indianapolis, June 23-25. Ex. Sec., Miss Ruth V. Kirk, 538 K of P Bldg., Indianapolis.

MAINE: Portland, March 10-11. Sec., Dr. Adam P. Leighton, 192 State St., Portland.

MASSACHUSETTS: *Examination.* Boston, Jan. 13-16. Sec., Dr Robert C. Cochrane, Room 37, State House, Boston.

MINNESOTA:* Minneapolis, Jan. 20-22. Sec., Dr. J. F. Du Bois, 230 Lowry Medical Arts Bldg., St. Paul 2.

MONTANA: *Examination.* Helena, April 7-8. *Reciprocity.* Helena, April 6. Sec., Dr. S. A. Cooney, 7 West 6th Ave., Helena.

NEBRASKA:* *Examination.* Omaha, June 1953. Director, Mr. Husted K. Watson, Room 1009 State Capitol Bldg., Lincoln 9.

NEVADA:* Carson City, Feb. 2. Dr. George H. Ross, 112 North Curry St., Carson City.

NEW JERSEY: Trenton, June 16-19. Sec., Dr. Earl S. Hallinger, 28 West State St., Trenton.

NEW YORK: Albany, Buffalo, New York and Syracuse, Jan. 27-30. Sec., Dr. Stiles D. Ezell, 23 S. Pearl St., Albany 7.

NORTH CAROLINA. *Reciprocity.* Winston Salem, Jan. 19. Sec., Dr. Joseph J. Combs, 716 Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, Jan. 7-9. *Reciprocity.* Grand Forks, Jan. 10. Sec., Dr. C. J. Glaspel, Grafton,

OKLAHOMA:* *Examination.* Oklahoma City, June 10-11. Sec., Dr. Clinton Gallaher, 813 Braniff Bldg., Oklahoma City.

OREGON:* *Examination.* Portland, Jan. 5-6. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

PENNSYLVANIA: *Examination.* Philadelphia, January. Acting Sec., Mrs. Marguerite G. Steiner, Box 911, Harrisburg.

RHODE ISLAND:* *Examination.* Providence, Jan. 8-9. Administrator, Division of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH DAKOTA:* Sioux Falls, Jan. 20-21. Exec. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

TEXAS:* Fort Worth, June 22-24. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Ft. Worth 2.

UTAH: *Examination.* Salt Lake City, July. Asst. Dir., Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City.

VERMONT: *Examination.* Burlington, Jan. 29-31. Sec., Dr. F. J. Lawliss, Richford.

WEST VIRGINIA: Charleston, Jan. 12-14. Sec., Dr. N. H. Dyer, State Office Bldg., No. 3, Charleston 5.

WISCONSIN: *Examination.* Madison, January 13-15. Sec., Dr. A. G. Kochler, 46 Washington Blvd., Oshkosh.

WYOMING: *Examination.* Cheyenne, Feb. 2. Examinations are regularly scheduled the first Monday of February, June and October of each year. Sec., Dr. Franklin D. Yoder, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: *Examination.* On application, Juneau or other towns in Territory as decided by Board. *Reciprocity.* On application. Sec., Dr. C. Earl Albrecht, Box 1931, Juneau.

COLORADO: Denver, March 4-5. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver 18.

FLORIDA: *Examination.* Gainesville, June 6. Sec., Mr. M. W. Emmel, Box 340, University of Florida, Gainesville.

IOWA: Des Moines, Jan. 13. Sec., Dr. Ben H. Peterson, Coe College, Cedar Rapids.

MICHIGAN: Detroit and Ann Arbor, Feb. 13-14. Sec., Mrs. Ann Baker, 423 W. Michigan Ave., Lansing.

MINNESOTA: Minneapolis, Jan. 6-7. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis.

NEBRASKA: Omaha, Jan. 13-14. Sec., Mr. Husted K. Watson, Room 1009 State Capitol Bldg., Lincoln 9.

OKLAHOMA: Oklahoma City, April 3. Sec., Dr. Clinton Gallaher 813 Braniff Bldg., Oklahoma City.

RHODE ISLAND: *Examination.* Providence, Feb. 11. Administrator, Division of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

TENNESSEE: *Examination.* Memphis, Dec. 31-Jan. 1. Sec., Dr. O. W. Hyman, 874 Union Ave., Memphis.

TEXAS: *Examination.* Dallas and Galveston, April. Sec., Bro. Raphael Wilson, 407 Perry Brooks Bldg., Austin.

* Basic Science Certificate required.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. George F. Lull, 535 North Dearborn St., Chicago 10, Secretary.

1953 Annual Session, New York, June 1-5.

1953 Clinical Session, St. Louis, Dec. 1-4.

1954 Annual Session, San Francisco, June 21-25.

1954 Clinical Session, Miami, Florida, Nov. 30-Dec. 3.

ANNUAL CONGRESS ON INDUSTRIAL HEALTH, Drake Hotel, Chicago, Jan. 20-22. Dr. Carl M. Peterson, 535 N. Dearborn St., Chicago 10, Secretary.

ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE, Palmer House, Chicago, Feb. 9-10. Dr. Donald G. Anderson, 535 North Dearborn St., Chicago, Secretary.

NATIONAL CONFERENCE ON RURAL HEALTH, Roanoke Hotel, Roanoke, Va., Feb. 27-28. Mrs. Arline Hibbard, 535 N. Dearborn St., Chicago 10, Secretary.

STUDENT AMERICAN MEDICAL ASSOCIATION, Sheraton Hotel, Chicago, Dec. 29-30. Mr. Russell F. Staudacher, 535 North Dearborn St., Executive Secretary.

AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS, Palmer House, Chicago. Jan. 24-29. Dr. John R. Norcross, 122 South Michigan Avenue, Chicago 3, Secretary.

AMERICAN COLLEGE OF RADIOLOGY, Palmer House, Chicago, Feb. 6. Mr. William C. Stronach, 20 North Wacker Drive, Chicago 6, Executive Secretary.

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY:

EASTERN SECTION, Hotel Syracuse, Syracuse, N. Y., Jan. 7. Dr. Francis W. Davison, Danville, Pa., Chairman.

MIDDLE SECTION, Drake Hotel, Chicago, Jan. 19. Dr. Ralph J. McQuiston, 20 North Meridian St., Indianapolis 4, Chairman.

SOUTHERN SECTION, Andrew Jackson Hotel, Nashville, Tenn., Jan. 12. Dr. Lester A. Brown, 490 Peachtree St., N.E., Atlanta 3, Ga., Chairman.

WESTERN SECTION, Elks Club, Los Angeles, Jan. 24. Dr. Howard P. House, 1136 West Sixth St., Los Angeles 14, Chairman.

AMERICAN PROTESTANT HOSPITAL ASSOCIATION, Palmer House, Chicago, Feb. 10-13. Mr. Albert G. Hahn, Protestant Deaconess Hospital, Evansville, Ind., Executive Secretary.

INTERNATIONAL POST-GRADUATE MEDICAL ASSEMBLY OF SOUTHWEST TEXAS, Municipal Auditorium, San Antonio, Texas, Jan. 27-29. Dr. John M. Smith Jr., P. O. Box 2445, San Antonio 6, Texas, Secretary.

NORTHWEST SOCIETY FOR CLINICAL RESEARCH, Seattle, Jan. 16-17. Dr. Arthur L. Rogers, 1216 S.W. Yamhill St., Portland 5, Ore., Secretary

REGIONAL MEETINGS, AMERICAN COLLEGE OF PHYSICIANS:

EASTERN PENNSYLVANIA, Philadelphia, Jan. 16. Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Executive Secretary.

SECTIONAL MEETINGS, AMERICAN COLLEGE OF SURGEONS:

CINCINNATI, The Netherland Plaza, Jan. 19-21. Dr. M. M. Zinninger, Cincinnati General Hospital, Cincinnati 29, Chairman.

SOCIETY OF UNIVERSITY SURGEONS, Washington University, St. Louis, Feb. 12-14. Dr. Clarence Dennis, Kings County Hospital, Brooklyn, N. Y., Secretary.

U. S. CHAPTER, INTERNATIONAL COLLEGE OF SURGEONS, SURGICAL DIVISION MEETINGS:

TRI-STATE ASSEMBLY OF TEXAS, Arkansas and Oklahoma, Adolphus Hotel, Dallas, Texas, Feb. 5-7. Dr. Curtice Rosser, 710 Medical Arts Bldg., Dallas, Texas, Chairman.

PENNSYLVANIA AND SURROUNDING STATES, Bellevue-Stratford Hotel, Philadelphia, Feb. 13-14. Dr. Moses Behrend, 225 South 17th St., Philadelphia, Chairman.

WESTERN SOCIETY FOR CLINICAL RESEARCH, Carmel, Calif., Jan. 30-31. Dr. Herbert N. Hultgren, Stanford Hospital, San Francisco 15, Secretary.

INTERNATIONAL

CONGRESS OF INTERNATIONAL LEAGUE AGAINST RHEUMATISM, Geneva and Zurich, Switzerland, Aug. 24-29, 1953. For information write: Dr. W. Tegner, The London Hospital, London E.1, England.

CONGRESS OF THE INTERNATIONAL SOCIETY OF SURGERY, Lisbon, Portugal, Sept. 15-20, 1953. Dr. L. Dejardin, 141, rue Belliard, Brussels, Belgium, General Secretary.

INTER-AMERICAN SESSION, AMERICAN College of Surgeons, Paulista Medical Association Bldg., Sao Paulo, Brazil, Feb. 9-12, 1953. Dr. Moacyr Eyck Alvaro, 1151 Conselacao, Sao Paulo, Brazil, Chairman.

INTERNATIONAL CONGRESS OF AUDIOLOGY, Groningen, Netherlands, June 5-6, 1953. Dr. Gunnar Holmgren, Strandvagen 5A, Stockholm, Sweden, President.

INTERNATIONAL CONGRESS OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY, Boston, Mass., U. S. A., Aug. 18-21, 1953. Dr. Robert S. Schwab, Massachusetts General Hospital, Boston 14, Mass., U. S. A., Secretary-General.

INTERNATIONAL CONGRESS FOR HISTORY OF SCIENCE, Jerusalem, Israel, August 3-7, 1953. Prof. F. S. Bodenheimer, Hebrew University, Jerusalem, Israel, President.

INTERNATIONAL CONGRESS ON MEDICAL LIBRARIANSHIP, London, England, July 20-25, 1953. Mr. W. R. LeFanu, % London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1, England, Chairman.

INTERNATIONAL CONGRESS OF MICROBIOLOGY, Rome, Italy, Sept. 6-12, 1953. For information write: Dr. V. Puntoni, Citta Universitaria, Rome, Italy.

INTERNATIONAL CONGRESS OF OTORHINOLARYNGOLOGY, Amsterdam, Netherlands, June 8-15, 1953. Dr. W. H. Struben, J. J. Viottastraat 1, Amsterdam, Netherlands, Secretary.

INTERNATIONAL CONGRESS OF PAEDIATRICS, Havana, Cuba, Oct. 12-17, 1953. Prof. Felix Hurtado, 5a Avenue 124, Miramar, Havana, Cuba, President.

INTERNATIONAL CONGRESS OF RADIO-BIOLOGY, Copenhagen, Denmark, July 14-25, 1953. Prof. Flemming Norgaard, Oster Voldgade 10, Copenhagen K, Denmark, Secretary General.

INTERNATIONAL CONGRESS OF RADIOLOGY, Copenhagen, Denmark, July 19-25, 1953. Professor Flemming Norgaard, 10 Oster Voldgade, Copenhagen K., Denmark, Secretary General.

INTERNATIONAL CONGRESS OF THALASSOTHERAPY, Dubrovnick, Yugoslavia, May 17-25, 1953. Prof. C. Plavaic, Mavrodne Republick 51, Belgrade, Yugoslavia, Secretary General.

INTERNATIONAL CONGRESSES OF TROPICAL MEDICINE AND MALARIA, Istanbul, Turkey, Aug. 28-Sept. 4, 1953. Professor Dr. Ihsan Sükrü Aksel, Tunel Meydam, Beyoglu, Istanbul, Turkey, General Secretary.

INTERNATIONAL FERTILITY ASSOCIATION, New York, N. Y., U. S. A., May 25-31, 1953. Dr. Abner I. Weisman, 1160 Fifth Avenue, New York 29, N. Y., U. S. A., Associate Secretary General.

INTERNATIONAL HOSPITAL CONGRESS, London, England, May 25-30, 1953. Capt. J. E. Stone, 10 Old Jewry, London, EC2, England, Hon. Secretary.

INTERNATIONAL LEPROSY CONGRESS, Madrid, Spain, Oct. 3-10, 1953. Dr. Felix Contreras, Moreto 15, Madrid, Spain, Secretary.

INTERNATIONAL PHYSIOLOGICAL CONGRESS, Montreal, Canada, Aug. 31-Sept. 4, 1953. Dr. A. S. V. Burgen, Dept. of Physiology, McGill University, Montreal, Canada, Secretary.

INTERNATIONAL UNION AGAINST CANCER AND INTERNATIONAL CANCER RESEARCH COMMISSION, Joint Meeting, Bombay, India, Dec. 28. Prof. Khanolkar, Tata Memorial Hospital, Bombay, India, President.

INTERNATIONAL VETERINARY CONGRESS, Stockholm, Sweden, Aug. 9-15, 1953. Prof. Axel Isaksson, Institute of Veterinary Medicine, Stockholm 50, Sweden, Secretary.

PAN AMERICAN CONGRESS OF THE MEDICAL PRESS, Buenos Aires, Argentine, July 12-16, 1953. Secretaria del Congress, 763 Uriburu, Buenos Aires, Argentine.

PAN AMERICAN MEDICAL ASSOCIATION, International Medical Cruise Congress, S. S. Nieuw Amsterdam, Jan. 7-19. Executive Offices, 745 Fifth Ave., New York 22, N. Y.

WORLD CONFERENCE ON MEDICAL EDUCATION, British Medical Association House, Tavistock Square, W.C.1, London, England, Aug. 24-29, 1953. Secretariat: World Medical Association, 2 East 103d St., New York 29, N. Y., U. S. A.

WORLD CONGRESS OF THE WORLD CONFEDERATION FOR PHYSICAL THERAPY, London, England, Sept. 7-12, 1953. Miss M. J. Neilson, Chartered Society of Physiotherapy, Tavistock House, South, Tavistock Square, London, W.C.1, England, Secretary

DEATHS

Dabney, Albert Smith ✦ Colonel, U. S. Army, retired, Greensburg, Pa.; born in Cadiz, Ky., Nov. 4, 1879; Vanderbilt University School of Medicine, Nashville, Tenn., 1904; formerly assistant professor of medicine at his alma mater; in 1943 became assistant dean at the University of Pittsburgh School of Medicine; in 1916 entered the federal service as a medical officer in the Tennessee National Guard and served on the Mexican border; during the following years served at various camps and stations, as well as with the American Expeditionary Forces in France during World War I and later in the Philippine Islands; commissioned in the regular Army, July 1, 1920; rose through various ranks to that of colonel on Feb. 1, 1942; retired Nov. 30, 1943; from 1928 to 1931 was assigned to the War Department general staff in Washington, D. C., and the following year graduated from the Army War College; from 1932 through 1935 was an instructor at the Infantry School, Fort Benning, Ga.; then went to the Surgeon General's Office as executive officer; on June 27, 1939, transferred to the Medical Field Service School at Carlisle Barracks, where he was director of the medical department equipment laboratory before becoming assistant commandant in January, 1942; member of the Mexican Military Surgeons Association and the Phi Chi and Sigma Alpha Epsilon fraternities; life member of the Association of Military Surgeons of the United States; fellow of the American College of Surgeons; with 27 years of service to his credit, held decorations from the American, British, French, and Haitian governments; on Sept. 15, 1943, was awarded the Legion of Merit; died Aug. 29, aged 72.

Keyser, Linwood Dickens ✦ Roanoke, Va.; born in Victoria, Texas, Sept. 26, 1893; Johns Hopkins University School of Medicine, Baltimore, 1918; specialist certified by the American Board of Urology; member of the American Association for the Advancement of Science, Johns Hopkins Surgical Society, Tri-State Medical Society of Virginia and the Carolinas, Southern Medical Association, Southwest Virginia Medical Society, Southeastern Surgical Congress, American Association of Genito-Urinary Surgeons, Alumni Association of Mayo Foundation, Sigma Xi, and the American Urological Association; fellow of the American College of Surgeons; past president of the Roanoke Academy of Medicine; one of the founders, past president, vice-president, and secretary-treasurer of the Virginia Urological Society; president of the Southwestern Branch of the American Urological Association; corresponding member of the Argentine Urological Society; served as first lieutenant in the medical reserve corps of the U. S. Army from 1918 to 1925; formerly a fellow at Mayo Foundation in Rochester, Minn.; for many years affiliated with Roanoke Hospital, where he was director of laboratory; consultant surgeon to Gill Memorial and Burrell Memorial hospitals from 1928 to 1950; died Oct. 12, aged 59, of chronic nephritis and rheumatic heart disease.

Mason, James Monroe ✦ Birmingham, Ala.; born in Marion, Ala., Nov. 21, 1871; Medical Department of Tulane University of Louisiana, New Orleans, 1899; professor of surgery at Medical College of Alabama from 1945 to 1949, when he became professor emeritus; member of the founders group of the American Board of Surgery; past president of the Medical Association of the State of Alabama, Jefferson County Medical Society, Birmingham Surgical Society, and the Southern Surgical Association; member of the Southeastern Surgical Congress and the American Surgical Association, of which he was vice-president; a founder, for many years a governor, and member of the board of regents of the American College of Surgeons, serving as a member of the advisory council until his death; chief surgeon and medical director of Alabama Power Company, chief surgeon of Birmingham Electric Company, and a member of the surgical staffs of St. Vincent's, Children's, and Jefferson-Hillman hospitals; in 1935, during the 100th anniversary celebration of Tulane University, was given the honorary degree of doctor of science; died Oct. 8, aged 80.

✦ Indicates Member of the American Medical Association.

Levy, Louis, Memphis, Tenn.; born in Paducah, Ky., Feb. 7, 1889; University of Tennessee College of Medicine, Memphis, 1910; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; formerly associate professor of otology, laryngology, and rhinology at his alma mater; member of the American Academy of Ophthalmology and Otolaryngology, American Laryngological, Rhinological and Otological Society, and the Association of Military Surgeons of the United States; life member of the American College of Surgeons; past president of the Memphis Symphony Society and the Memphis Chapter of the Reserve Officers Association; one of the founders and chief-of-staff, Memphis Eye, Ear, Nose and Throat Hospital; affiliated with Crippled Children's Hospital School, and Hospital for Crippled Adults; on the visiting staffs of Methodist, St. Joseph, John Gaston, and Baptist Memorial hospitals; died Oct. 20, aged 63, of a heart attack.

Johnson, Aldis Adelbert ✦ Council Bluffs, Iowa; born in Maysville, Pa., June 16, 1880; Western Reserve University Medical Department, Cleveland, 1912; specialist certified by the American Board of Internal Medicine; member of the American Society of Clinical Pathologists and the American Heart Association; fellow of the American College of Physicians; past president of the Pottawattamie County Medical Society, Iowa Clinical Society, and the Iowa State Medical Society; formerly chairman of the Iowa State Board of Medical Examiners, of which he had been a member for many years; at one time vice-president of the Federation of State Medical Boards of the United States; formerly on the faculty of the University of Nebraska College of Medicine in Omaha; served with the American Expeditionary Forces overseas during World War I; on the staff of the Jennie Edmundson Hospital; died in the Bishop Clarkson Memorial Hospital in Omaha Oct. 25, aged 72, of heart failure.

Wolcott, W. Eugene ✦ Des Moines, Iowa; born in Battle Creek, Iowa, Aug. 13, 1885; State University of Iowa College of Medicine, Iowa City, 1910; specialist certified by the American Board of Orthopaedic Surgery; member of the American Orthopaedic Association and Clinical Orthopaedic Society; fellow of the American College of Surgeons; president of the Iowa Orthopaedic Society in 1941, and also served as secretary; served with the British and American forces during World War I; at one time assistant professor of orthopedics at Creighton University School of Medicine in Omaha; instructor of orthopedic surgery, University of Virginia Department of Medicine, Charlottesville, Va.; affiliated with Broadlawns Polk County Hospital, Iowa Methodist Hospital, and Mercy Hospital; died in St. Bernard's Hospital, Council Bluffs, Sept. 3, aged 67, of cerebral thrombosis.

Mitchell, Albert Melvin ✦ Terre Haute, Ind.; born in Terre Haute, Ind., in 1889; University of Louisville (Ky.) School of Medicine, 1913; in 1949 a member of the House of Delegates of the American Medical Association; founder and played an active role in sponsoring the Grass Roots Conferences held in conjunction with the American Medical Association meetings; served as chairman of the Grass Roots Conference each year until the meetings were discontinued with his initial illness a year or more ago; in addition to serving as an alternate delegate from Indiana to the American Medical Association House of Delegates, sponsored the county medical society conferences in his home state for more than 20 years; past president of the Indiana State Medical Association; for many years secretary of the Vigo County Medical Society; affiliated with Union Hospital; died Nov. 10, aged 63, of heart disease.

Mackay, Albert Edward ✦ Portland, Ore.; born in Toronto, Canada, June 15, 1863; University of Toronto Faculty of Medicine and Trinity Medical College, Toronto, Canada, 1887; specialist certified by the American Board of Urology; member of the North Pacific Surgical Association and the American Urological Association; fellow of the American College of Surgeons; professor emeritus of urology at the University of Oregon

Medical School; past president of the Oregon State Medical Society, Multnomah County Medical Society, Portland Academy of Medicine, and the western branch of the American Urological Association; served on the staffs of the Multnomah and Good Samaritan hospitals; in 1941 received the honorary degree of doctor of science from the University of Oregon Medical School; died Nov. 1, aged 89.

Sawyer, Leroy Lee Jr. ✠ Washington, D. C.; born in Great Bridge, Va., Dec. 2, 1898; Medical College of Virginia, Richmond, 1922; assistant clinical professor of otorhinolaryngology at George Washington University School of Medicine; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; affiliated with Central Dispensary and Emergency Hospital, Children's Hospital, Episcopal Eye, Ear and Throat Hospital, Gallinger Municipal Hospital, and George Washington University Hospital; died Nov. 9, aged 53.

Hare, John Herbert ✠ Evansville, Ind.; born in Sheridan, Ind., May 24, 1893; Indiana University School of Medicine, Indianapolis, 1916; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; in 1921 president of the Vanderburgh County Medical Society; served during World War I; at one time state health commissioner; superintendent of the Evansville State Hospital; affiliated with St. Mary's Hospital, Protestant Deaconess Hospital, and Welborn Memorial Baptist Hospital, where he died Oct. 31, aged 59, of a cerebrovascular accident.

Anderson, Arvid Edgar ✠ Aberdeen, Wash.; University of Oregon Medical School, Portland, 1914; in 1930 president of the Washington State Medical Association; past president of the Grays Harbor Medical Society; member of the American Association of Railway Surgeons; served during World War I; affiliated with St. Joseph Hospital; died Oct. 23, aged 61, of coronary thrombosis.

Arnold, Asa Martin ✠ Claremore, Okla.; Louisville (Ky.) Medical College, 1889; died Oct. 20, aged 88.

Cooke, Robert Page ✠ Lexington, Va.; University of Virginia Department of Medicine, Charlottesville, 1897; served as health officer of Rockbridge County and of Accomac and Lexington; received a gold medal from Congress for his public service during the experimental investigation of yellow fever by the Walter Reed Army Commission in Cuba in 1900; then an acting assistant surgeon, he volunteered to expose himself to fomites during the investigation; died Oct. 27, aged 78, of uremia.

Davis, Robert Lee, McKinney, Texas; Memphis (Tenn.) Hospital Medical College, 1892; served as health officer of McKinney and of Collin County; died Oct. 7, aged 86.

de Yoanna, Aurelius ✠ Brooklyn; Université de Paris Faculté de Médecine, France, 1892; Bellevue Hospital Medical College, New York, 1897; died Sept. 14, aged 91.

Dieterich, William Clay, Mankato, Minn.; Homeopathic Medical College of Missouri, St. Louis, 1895; died in Worthington recently, aged 80.

Estrin, Joseph Zachary ✠ Cody, Wyo.; University of Michigan Medical School, Ann Arbor, 1929; member of the Nevada State Medical Association and the American Trudeau Society; specialist certified by the American Board of Radiology; served during World War II; formerly radiologist at Washoe Medical Center in Reno, Nev.; died in Memorial Hospital Oct. 9, aged 48, of malignant hypertension.

Evans, John Thomas, Middlesboro, Ky.; Hospital College of Medicine, Louisville, 1903; died Oct. 2, aged 75.

Fitch, Willis Bryan ✠ St. Johnsbury, Vt.; University of Maryland School of Medicine, Baltimore, 1903; also a graduate in pharmacy; Associate Fellow of the American Medical Association; affiliated with Brightlook Hospital; founder of the Fitch Clinic; died Oct. 16, aged 74, of carcinoma of the bladder.

Fontaine, William James ✠ Jones Prairie, Texas; University of Texas School of Medicine, Galveston, 1898; died in St. Edward Hospital, Cameron, Oct. 22, aged 77, of arteriosclerotic heart disease.

Foster, Ira Curtin, Steubenville, Ohio; University of the South Medical Department, Sewanee, Tenn., 1895; died Sept. 30, aged 83.

Fowle, Frederick Filer, Shorewood, Wis.; Rush Medical College, Chicago, 1900; formerly affiliated with Milwaukee County Hospital for Mental Diseases in Wauwatosa; died Oct. 19, aged 84, of hypostatic pneumonia and arteriosclerotic heart disease.

Greason, Woodard B., Excelsior Springs, Mo.; University Medical College of Kansas City, 1897; died in Excelsior Springs Sanitarium and Hospital Oct. 21, aged 79, of coronary occlusion.

Greenwood, Mitchell, Wilmington, Del.; Hahnemann Medical College and Hospital of Philadelphia, 1898; died in Bellefonte Sept. 16, aged 86.

Grob, Arthur R. F. ✠ Milwaukee; the Hahnemann Medical College and Hospital, Chicago, 1888; National Medical University, Chicago, 1899; served on the board of trustees of the Johnston Emergency Hospital; died Oct. 22, aged 85, of carcinoma of the prostate.

Groom, Walter W., McAlester, Okla. (licensed in Oklahoma by years of practice); died Oct. 2, aged 72, of cerebral thrombosis.

Haeffner, Albert William ✠ Berkeley, Ill.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1906; died in Elgin (Ill.) State Hospital Nov. 4, aged 71, of arteriosclerotic and degenerative heart disease.

Hamrick, Robert Hampton ✠ Birmingham, Ala.; Atlanta Medical College, 1895; past president of the Jefferson County Medical Society; died Oct. 25, aged 85, of coronary heart disease.

Hanna, James Francis ✠ Fargo, N. D.; Marquette University School of Medicine, Milwaukee, 1913; past president of the North Dakota State Medical Association and the North Dakota Society of Obstetrics and Gynecology; member of the Central Association of Obstetricians and Gynecologists; specialist certified by the American Board of Obstetrics and Gynecology; affiliated with St. John's and St. Luke's hospitals; died Oct. 14, aged 66, of cerebral hemorrhage.

Harman, William Cloud ✠ Dolphin, Va.; Maryland Medical College, Baltimore, 1913; an Associate Fellow of the American Medical Association; died in Johnston-Willis Hospital in Richmond, Oct. 13, aged 76, of injuries received in an automobile accident.

Hays, Edward R. ✠ Danbury, Conn.; born in 1885; Ensworth Medical College, St. Joseph, Mo., 1906; member of the Nebraska State Medical Association; formerly practiced in Falls City, Neb., where he was city physician and member of the board of health; in 1945 elected director of health education for the Evanston (Ill.) schools; in 1930 the first physician to receive the Noguchi gold medal, presented to the physician in Nebraska who had done the most to advance the cause of preventive medicine; died in St. Louis Sept. 8, aged 67, of a heart attack.

Herring, Alvah Livingston ✠ Richmond, Va.; University College of Medicine, Richmond, 1910; fellow of the American College of Surgeons; member of the Richmond Academy of Medicine; served overseas during World War I; affiliated with Sheltering Arms Hospital, Richmond Community Hospital, and Retreat for the Sick; for many years president of the Grace Hospital, where he was attending surgeon; died Oct. 24, aged 66, of coronary thrombosis.

Hilliard, Joshua, Manahawkin, N. J.; College of Physicians and Surgeons, Baltimore, 1901; founder and charter president of the Ocean County Historical Society; for many years vice-president of the First National Bank of Barnegat; died in Atlantic City (N. J.) Hospital Sept. 26, aged 79, of acute myocardial infarction.

Hirsh, Joseph Emmet ✠ Birmingham, Ala.; University of Pennsylvania School of Medicine, Philadelphia, 1922; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; professor of clinical medicine, Medical College of Alabama; served on the staff of the Hillman Hospital; official team physician for the Crimson Tide; died in Baton Rouge, La., Sept. 27, aged 54, of coronary thrombosis, while attending the Alabama-Louisiana State University football game.

Holman, Albert William ✦ Portland, Ore.; University of Oregon Medical School, Portland, 1921; vice-chairman, 1951-1952, chairman 1952-1953, Section on Obstetrics and Gynecology, American Medical Association; specialist certified by the American Board of Obstetrics and Gynecology; member of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons and the Pacific Coast Society of Obstetrics and Gynecology; affiliated with St. Vincent's Hospital; died Oct. 28, aged 56.

Johnson, Edward Hinman ✦ Peabody, Kan.; College of Physicians and Surgeons, Medical Department of the Kansas City University, Kansas City, 1902; veteran of the Spanish-American War and World War I; local surgeon for the Atchison, Topeka and Santa Fe and Rock Island railroads; died in Walton Oct. 23, aged 78, of coronary thrombosis.

Johnston, Charles Wesley, Greenville, N. H.; College of Physicians and Surgeons, Boston, 1915; died in Boston Sept. 5, aged 63.

Kay, Milton Boyd ✦ Miami Beach, Fla.; University of Pennsylvania Department of Medicine, Philadelphia, 1905; served during World War I; at one time on the faculty of Detroit College of Medicine and Surgery; died Oct. 13, aged 71, of chronic myelogenous leukemia.

Keith, Claude Hill, Townsend, Del.; University of Vermont College of Medicine, Burlington, 1922; died Sept. 2, aged 65, of coronary thrombosis.

Kimble, Thaddeus Carey ✦ Miltonvale, Kan.; St. Louis College of Physicians and Surgeons, 1898; served one term as a representative in the state legislature; for many years on the school board; local physician and surgeon for Union Pacific and Santa Fe railroads; died in Topeka Aug. 28, aged 76.

King, James R. ✦ Silver Lake, Ind.; Baltimore University School of Medicine, 1893; died in the Murphy Medical Center, Warsaw, Sept. 15, aged 83, of heart disease.

Kingsley, Glenn Edwin ✦ Lorain, Ohio; Ohio State University College of Medicine, Columbus, 1936; served during World War II; died in Cleveland Oct. 22, aged 42, of cirrhosis of the liver.

Knichel, Joseph, Maplewood, Mo.; Marion-Sims-Beaumont Medical College, St. Louis, 1902; died Nov. 1, aged 78, of hypertensive heart disease with bronchial asthma.

Langworthy, Orthello Sidney, Hamilton, N. Y.; University of the City of New York Medical Department, 1891; formerly member of the school board; died in Baltimore Sept. 30, aged 86, of coronary occlusion.

Lanier, John Roy, Twin City, Ga.; Medical College of Georgia, Augusta, 1928; died in Swainsboro recently, aged 51, of cirrhosis of the liver and myocarditis.

Leicht, Oswald, Winona, Minn.; Northwestern University Medical School, Chicago, 1898; died in St. Nicholas Hospital, Sheboygan, Wis., Oct. 16, aged 77, of myocardial infarction and pulmonary edema.

Love, John King ✦ Easton, Pa.; Jefferson Medical College of Philadelphia, 1897; served on the staff of the Easton Hospital; died in Clinton, N. J., Oct. 31, aged 84, of carcinoma of the lung.

Maag, William Dovey, Jeffersonville, Ohio; Ohio State University College of Medicine, Columbus, 1917; served as county health commissioner; died Oct. 16, aged 62.

McPhail, Walter Neil ✦ Missoula, Mont.; McGill University Faculty of Medicine, Montreal, Canada, 1923; affiliated with St. Patrick and Memorial hospitals; died Aug. 31, aged 57.

Mammarella, Settembre, Philadelphia; Medico-Chirurgical College of Philadelphia, 1915; died in Methodist Hospital Oct. 18, aged 59, of coronary infarction.

Merten, Peter Joseph ✦ Milwaukee; Chicago College of Medicine and Surgery, 1909; died in St. Mary's Hospital Oct. 14, aged 73, of cerebral hemorrhage.

Miller, Charles R., Harrisburg, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1887; died Oct. 18, aged 94, of cerebral thrombosis.

Miller, Hugh ✦ Kansas City, Mo.; Kansas City Medical College, 1897; member of the American Academy of Ophthalmology and Otolaryngology; affiliated with St. Mary's Hospital, where he died Sept. 11, aged 85, of myocarditis and prostatic hypertrophy.

Mogan, William Edward ✦ Denver; John A. Creighton Medical College, Omaha, 1912; served as chief of staff of St. Anthony's Hospital, where he died Oct. 22, aged 64, of bacteremia.

Montgomery, James Redman ✦ Owensville, Ind.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1904; affiliated with Gibson General Hospital in Princeton; died Oct. 29, aged 73, of coronary thrombosis.

Moschelle, Judson D., Indianapolis; Medical College of Indiana, Indianapolis, 1902; died in Methodist Hospital Oct. 10, aged 74, of cerebral hemorrhage.

Newton, Louis ✦ Bridgeport, Conn.; New York Homeopathic Medical College and Flower Hospital, 1931; member of the New England Obstetrical and Gynecological Society; fellow of the American College of Surgeons; specialist certified by the American Board of Obstetrics and Gynecology; affiliated with Bridgeport and Englewood hospitals; died Oct. 18, aged 50, of bronchopneumonia.

Pernokis, Evans William ✦ Chicago; Harvard Medical School, Boston, 1923; clinical associate professor of medicine (Rush), University of Illinois College of Medicine; certified by the National Board of Medical Examiners; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; served during World Wars I and II; affiliated with Cook County Hospital and the Presbyterian Hospital, where he died Nov. 9, aged 54, of coronary artery sclerosis.

Roark, John Paul ✦ Chicago; Rush Medical College, Chicago, 1889; an Associate Fellow of the American Medical Association; died in the Mercy Hospital, Gary, Ind., Oct. 19, aged 88.

Rogers, Richard Ovid ✦ Bluefield, W. Va.; Medical College of Virginia, Richmond, 1907; member of the Industrial Medical Association; past president of the West Virginia State Medical Association, Mercer County Medical Society, and the Hospital Association of West Virginia; served overseas during World War I and was attached to Great Britain's Royal Army Medical Corps; for many years medical director of the Bluefield Sanitarium; died Nov. 4, aged 70, of a heart attack.

Sanford, Frederick Clyde, Clare, Mich.; University of Michigan Homeopathic Medical School, Ann Arbor, 1890; for many years health officer and member of the board of education; died Oct. 21, aged 88.

Schutz, Edwin George, Los Angeles; Long Island College Hospital, Brooklyn, 1898; died in Queen of Angels Hospital Oct. 2, aged 77.

Senn, Hugh Boozer ✦ Newberry, S. C.; Medical College of the State of South Carolina, Charleston, 1913; past president of the Newberry County Medical Society and of the South Carolina Public Health Association; for many years connected with South Carolina State Board of Health and later with Georgia State Board of Health; died Oct. 6, aged 64, of Hodgkin's disease.

Stanton, Edward Daniel, Reedsburg, Wis.; University of Wisconsin Medical School, Madison, 1928; for many years member of the staff of Reedsburg Municipal Hospital; died Oct. 26, aged 52, of hepatitis.

Truxaw, John Wenceslaus ✦ Anaheim, Calif.; University of California Medical School, San Francisco, 1911; affiliated with St. Joseph Hospital in Orange, where he died Oct. 23, aged 69.

Tweedy, George J. ✦ Winona, Minn.; Trinity Medical College, Toronto, Canada, 1890; fellow of the American College of Surgeons; member of the staff of Winona General Hospital; died recently, aged 90.

Van Winkle, Peter, La Jolla, Calif.; Washington University School of Medicine, St. Louis, 1892; died Oct. 24, aged 84, of cerebral hemorrhage.

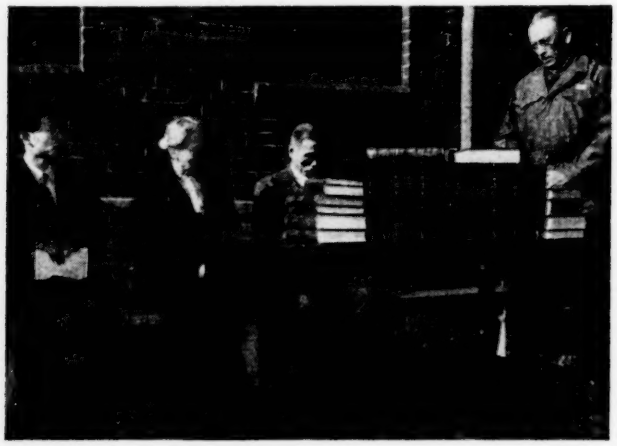
Yamashiro, Matsuzu Martin ✦ Honolulu, Hawaii; State University of Iowa College of Medicine, Iowa City, 1930; died Aug. 18, aged 52, of a heart attack.

GOVERNMENT SERVICES

ARMY

Medical Instructors Conference.—The fifth conference for briefing Army medical instructors in developments in field medicine and trends in training philosophy and method was held Dec. 1-3 at the Medical Field Service School, Fort Sam Houston, Texas. Major Gen. Silas B. Hays, Deputy Surgeon General, spoke on "The Practice of Economy in the Army Medical Service." Papers were read on the operation of the Medical Field Service School, Medical Service Graduate School, and Medical Replacement Training Center; the status of Medical Service extension courses, current medical training literature, and reviews of medical instruction at the Command and General Staff College and the chemical corps, armored, infantry, and artillery schools. Among the more specialized subjects presented were "Current Korean Experiences in Anxiety States," "Thermal Burns in Modern Warfare," "Preventive Medicine in the Conservation of Combat Manpower," "Recent Concepts in the Care of the Severely Wounded," and "Professional Training for Medical Preparedness." The conference brought together a large group of officers.

Medical Books for Korea.—This picture shows Brig. Gen. L. Holmes Ginn Jr., then Colonel, Eighth Army Surgeon, presenting medical books and journals to Choi Pyung How, president of the student body, Dr. F. J. Murray, assistant superintendent,



and Dr. Kim Myung Sung, president of the Severance Union Medical College and Hospital, Seoul, Korea. These books comprise one of many shipments received from physicians and friends following General Ginn's appeal for medical literature for the school.

ATOMIC ENERGY COMMISSION

Cosmotron Dedicated at Brookhaven.—The most powerful accelerator of nuclear particles, the "cosmotron," was dedicated Dec. 15 in ceremonies at Brookhaven National Laboratory, Upton, Long Island, N. Y. Gordon Dean and Henry D. Smyth, members of the Atomic Energy Commission, delivered addresses. Detlev Bronk, president of Johns Hopkins University, spoke on behalf of the nine universities represented in Associated Universities, Inc., the nonprofit corporation that operates Brookhaven under contract with the Commission. Other speakers were Lloyd V. Berkner, president of Associated Universities, Inc.; Leland J. Haworth, director of Brookhaven National Laboratory; E. L. Van Horn, manager of the Atomic Energy Commission office for the Brookhaven area; and George B. Collins, chairman of the laboratory's accelerator department. The design of the cosmotron began in 1947. On May 20, 1952, the machine speeded up protons to an energy of 1.3 billion volts, about three times that achieved by the most powerful cyclotrons. Modifications are now being completed that will enable the machine to deliver 2 to 3 billion volt energies on a routine basis for research beginning in 1953.

PUBLIC HEALTH SERVICE

Program for Control of Diarrheal Diseases.—For three years, the Communicable Disease Center, Public Health Service, has conducted a program for the control of dysentery and diarrheal diseases, with emphasis on the role of flies in transmitting the diseases. From 1941 to 1949, dysentery-diarrheal diseases caused over 83,000 deaths in the under-2-years age group, an average of over 9,000 deaths per year. The purpose of the program is to provide guidance and to demonstrate techniques by which communities can develop their own fly control projects. Seven demonstration projects were set up, two each in Arizona, New Mexico, and Texas, and one in Kentucky. The basic method by which the fly problem is attacked in these communities is by improvement and intensification of measures practiced over the past 50 years: community education, provision of adequate sanitation facilities to eliminate fly breeding sources, and spraying or chemical control. Since the start of the program, 34 additional cities have adopted the principles of the program, in whole or in part, under completely local sponsorship. The Communicable Disease Center has aided some of these communities with technical guidance, use of fly control educational films, and literature on community fly control operations.

Study of Health Programs.—The Public Health Service, assisted by the American Public Health Association, has undertaken a study of regional medical care and health programs in the United States. These voluntary programs, inaugurated in increasing numbers in the past two decades, aim to improve medical care and hospital services within the area of influence of a medical teaching center. The programs try to achieve this improvement through coordination of the various resources of the medical center with the medical, hospital, and health resources of the communities in the area. The Public Health Service obtained the consent of 12 such programs in this country for inclusion in the study. From each of the 12 information is being gathered on its objectives, membership and area coverage, organization, operational methods, volume of services, costs, and problems. On completion of the study a report of findings will be published.

Personal.—Dr. Francis J. Weber has been appointed medical director of Public Health Service Region IX, Denver. Dr. Weber, formerly director of Region IV, Cleveland, replaces Dr. Aaron Christensen, who was recently named chief of the Division of State Grants in Washington. Serving as acting director of the Cleveland office is Dr. Welby W. Bigelow.——At the request of the World Health Organization, Dr. Seward E. Miller, chief of the Division of Occupational Health, Public Health Service, has accepted a five year appointment as a special consultant on the joint WHO-ILO Expert Advisory Panel on Social and Occupational Health. The first job that WHO asked Dr. Miller to do under this appointment was to participate in a regional European seminar on occupational health in Leyden, Netherlands, Nov. 30 to Dec. 9, 1952. Dr. Miller presented a paper on "The Organization of Occupational Health Programs in Small Plants," covering particularly the coordination of inplant occupational health service with community public health programs, the growth of union health centers, and the various techniques.——After 36 years in the Public Health Service, Dr. Fred T. Foard retired Oct. 31 and will become director of the division of epidemiology for the North Carolina State Department of Health.

FOREIGN LETTERS

BELGIUM

Banti's Disease.—An extraordinary session of the Belgian Society of Gastroenterology was devoted to the study of Banti's syndrome and portal hypertension. Remouchamps, Gallus, and Cloquet studied all the factors in portal hypertension, as well as extrahepatic organic portal stasis, the localizations of which they have analyzed. They reviewed the arguments of the adversaries and the partisans of the concept of Banti's disease as a pathological entity and of the Banti-like syndromes. There are various syndromes of portal hypertension and similarly various splenomegalies, for which they draw up a scheme of differential diagnoses, and among which Banti's disease and the Banti-like syndromes are found.

The anatomicopathological data were discussed by Dustin, who stated that no lesion is in itself characteristic of Banti's disease; the term fibrocongestive hypertrophy is a better term. One notes, also, a reticular hyperplasia and a diffuse fibrosis of the red pulp. The fibrosis is principally periarterial, while the vascular wall is but little altered.

The clinical problem, the laboratory examinations, and the functional tests were discussed by Masure and Sonnet, while Brombart gave the results of radiographic study. Radiological demonstration of esophageal varices is often the first sign of portal hypertension not yet clinically recognizable. Boulvin and Chevalier pointed out the great importance of portal manometry and venography, which can now be carried out preoperatively without laparotomy by the transparietal splenic route. Lastly, a final technique of exploration of the portal system was described: postmortem portal radiomanometry, which will provide a great deal of information on the syndrome of portal hypertension and the normal and pathological intrahepatic and extrahepatic circulatory systems.

The general conclusions were stated by Brohee and Lecluyse: there is no such entity as Banti's disease. Banti's syndrome groups a number of affections that are damaging to the splenoportal system: the fibrocongestive splenomegalies. The splenomegaly is the result of portal hypertension. Therefore the problems of fibrosis, of a sclerosing factor, and of hormones especially should be studied.

Study of Paranormal Phenomena.—In 1948, a Belgian Committee for the Scientific Investigation of Phenomena Reputed to Be Paranormal was formed. Naturalists, mathematicians, astronomers, geologists, criminologists, physicians, archaeologists, historians, and ethnologists were invited to become members. The secretary gave a report on the first groups of investigations in the *Archiva Medica Belgica;* they concern 34 persons, reputed to be *radiesthésistes,* clairvoyants, spiritists, astrologists, and numerologists. Although the examination has disclosed nothing of any importance so far, the committee has been astonished at the ignorance and the naïveté (prelogical mentality) of those who claim to possess paranormal gifts; for example, it cites the supposed ability of *radiesthésistes* to distinguish pure water from polluted water. Experimental controls are never used, although this would be very easy to do. The committee is continuing its efforts, both in articles and in addresses, to put the public on guard against the activities, often notoriety-seeking and always self-interested, of all such spiritists and occultists.

Esophageal Perforations.—Before the Belgian Society of Gastroenterology, Orban and Foret presented a study on the diagnosis and treatment of recent esophageal perforations. These are the result of endoscopy in 65% of the cases and are caused by incarceration of a foreign body in less than 30%. Ulceration and erosion usually occur first. When symptoms are believed to be due to ulceration, then rest, methantheline bromide (banthine®), continuous aspiration of secretions, and antibiotics should be prescribed. If the perforation is complete, there is stabbing pain followed by signs of mediastinitis and pleuritis. The diagnosis is made by clinical and radiological examination (presence of gas, diaphragmatic rigidity): a few drops of iodized oil (lipiodol®) are enough in most cases to assure good visualization of the esophagus and of the perforation. Barium should not be used. Esophagoscopy, which is too dangerous at this time, must not be performed. The only therapy is surgical: (1) mediastinal drainage; (2) drainage of the pleura; and (3) suture of the perforation, if this is necessary and feasible (excision may be required).

Osteochondritis.—The Belgian Society of Orthopedics and Surgery of the Motor Apparatus devoted an extraordinary session to the study of the pathogenesis and classification of the diverse affections classed under the name of osteochondritis. R. Soeur presented a definition and clinical summary of osteochondritis. Limiting himself to osteochondritis of the hip, he reviewed the history and the gross and microscopic aspect of the lesions. Then he advanced the theory that the antagonism of the valgus-producing and varus-producing muscles is the *primum movens* of osteochondritis, the valgus-producing muscles being usually predominant. The therapeutic corollary is closure by osteotomy of the angle of inclination of the femur. He recognized the fact that this is not a final solution and that the hypothesis, which is original with him, must be verified.

J. Simonart discussed the localizations of osteochondritis (hip, tibia, calcaneus, tarsus, and metatarsus) and summarized the clinical theories dealing with the roles of calcium, infection, rickets, and congenital factors. E. Sorrel of Paris pointed out that certain conditions regarded by some as osteochondritis actually belong to a "dystrophic syndrome of growth." Broca, at the beginning of this century, had already defined this anatomicoclinical entity. It is characterized by (1) the time of its appearance (growth and puberty); (2) the anatomic substratum (softening and decalcification), which leads to (3) deformities, which are definitive. The speaker thought that an endocrine dysfunction was at the root of all these disturbances.

The vascular theory of origin of osteochondritis (Axhausen, Leriche) would imply an infarct of several vascular branches, causing disturbances over a wide territory, which is not the case. The traumatic theory has several adherents, considering that the child is often subject to minor injuries; however, it is difficult to imagine that a traumatic factor could produce section of the arteries at the level of the cartilage. The variety of the theories set forth shows clearly that Soeur's definition deserves to be retained: Osteochondritis is an aseptic necrosis of the bone that occurs in the course of growth, at the centers of ossification, primary or secondary. It evolves spontaneously toward cure but often at the expense of bone deformity.

Dangerous Vacations.—Masson recently has published an article in the *Scalpel* on the danger that group vacations for children may present. The question arose in connection with a request for placement of children in vacation homes, either near the sea or in Switzerland. It was not, therefore, a question of medical displacement, as in the case of a stay in a colony or preventorium.

The author carried out systematic radiological and clinical examinations. He found that 3% of the children examined gave radiological pulmonary pictures worthy of attention; of these, one-third had substantial lesions requiring therapy and one-third gave radiological pulmonary pictures of such a nature that exposure to sunshine would probably be injurious to them. He concluded that a sojourn in vacation camps, with their inevitable sunbaths, would have been dangerous for some children and certainly injurious to others. Since, in Belgium, some hundreds of thousands of children spend their school vacations in the open air, the author wished to make his findings known to draw attention to the potential danger of unconsidered sun cures.

The items in these letters are contributed by regular correspondents in the various foreign countries.

ITALY

Convention on Rheumatology.—At the sixth convention of the Italian Society of Rheumatology in Taormina, the first report was on fibrositis and was given by Professor Pisani, from the University of Florence. This disease is common in England, America, and Scandinavia, but it is also found in France and Italy. Professor Pisani suggested an anatomic and a clinical classification, dividing the anatomic classification into various groups, according to whether the white connective tissue (white fibrositis) or the subcutaneous connective tissue (adipose fibrositis, panniculitis, or cellulitis) is more impaired. The main symptoms, according to Professor Pisani, are fibrositic nodules and pain. He reported some cases that indicate a form of the disease that he would call serum nodular fibrositis. He cited another clinical form that he would classify as subscapular and that is unrelated to the common thoracic fibrosites. Among the latter, the pseudoanginal form is of particular interest.

In discussing the etiology, Professor Pisani cited the relationship of fibrositis to acute articular rheumatism and to primary chronic polyarthritis and discussed the importance of hepatic insufficiency, neuroendocrine changes, and allergic diathesis. Among the various causative factors he mentioned metabolic and "bioergic" changes. The speaker also discussed pelvic cellulitis and fat hernias of Copeman, which are similar to fibrositis.

Cortisone in Rheumatic Diseases.—The second paper, on the use of cortisone in the rheumatic diseases, was read by Professors Villa and Ballavio and Dr. Sala, from Milan. As the result of research done in the biological field, a complex series of biopathological phenomena has been attributed to the action of cortisone, among which are the inhibition of development of granulomatous tissue and the inhibition of allergic and other reactions to abnormal stimuli, as in antiphlogistic action. The clinical and therapeutic activity of cortisone is also promising.

In the study of the various physiological properties of the hormone, for example, it has been found that cortisone does not cause significant changes in the basal use of oxygen but it does increase the respiratory quotient. Cortisone affects the carbohydrate metabolism in various ways; it facilitates the transformation of proteins into glycides, and it lowers the renal threshold of glucose. In the person with a normal carbohydrate equilibrium, cortisone does not usually influence the metabolism of carbohydrates; it does, however, aggravate the disequilibrium in a diabetic. In the metabolism of lipids, cortisone increases the content of cholesterol, phospholipids, and fatty acids in the plasma. Cortisone also produces a negative protein balance and tends to cause retention of water and sodium and loss of potassium.

Indications for cortisone therapy in the rheumatological field are numerous, but in practice they are limited to rheumatic disease and primary chronic polyarthritis. Cortisone influences the general and local symptoms of the acute rheumatic attack in a constant and complete way. The main problem with this hormone lies in the treatment of rheumatic carditis; the early use of the drug in this disease may aid in the prevention of cardiac localizations. In an acute carditis already present, cortisone may reverse the symptoms, dramatically in some cases and to some degree in others. Its value is doubtful in some cases, such as in endocarditis. Evolutive rheumatic carditis is favorably influenced by this therapy. Improvement in the clinical signs is accompanied by improvement in laboratory findings.

Cortisone is also being used in primary chronic polyarthritis. Recent literature and the personal experience of the speakers showed that in most cases prolonged therapy is possible by the continued use of a maintenance dose. All the other indications for cortisone therapy in rheumatic diseases must be considered for the present to be still in the experimental phase, except for its use in gout, arthritis deformans of the hip, and scapulohumeral periarthritis, in which there are, nevertheless, limitations and methods of treatment peculiar to these diseases.

Arthritis Deformans.—The third report, which concerned arthritis deformans of the hip, was read by Prof. Marino Zuco, director of the orthopedic clinic of the University of Rome. The various forms of chronic arthritis of the hip, with their characteristic anatomic and histological alterations, present various clinical pictures, according to the origin and phase of the disease and manifestations of pain, contraction, rigidity, and deformity of the morphological elements that constitute an articulation.

The therapeutic problems with which orthopedic surgery is concerned in this disease arise according to the disturbances and the alterations that the various clinical forms of arthritis have caused or will cause, more or less rapidly. Various surgical treatments are suggested that are designed to alter the structure or function of the joint. Professor Zuco stressed the value of those means that are available today in the orthopedic surgery of arthritis deformans of the hip. These techniques will undoubtedly be improved.

Treatment of Pulmonary Tuberculosis.—At a meeting of the medical and surgical society of the Romagna region, the results of treatment of pulmonary tuberculosis with isonicotinic acid hydrazide were reported.

Professor D'Arcangelo and co-workers from the sanatorium of Forlí recalled the first reports on this subject by Robitzek and Selikoff in America, the reports from the German convention of Wiesbaden, and the reports of the medical society of Milan, Rome, Naples, and Bologna. The speakers reported on their own experience with 169 patients, of whom 52 were treated for from 30 to 50 days. These patients were among those whose condition was severest. The new drug had a favorable action on the general symptoms, fever, sputum, appetite, and weight. They stressed that during the first days of treatment the patients underwent a relapse consisting of elevation of temperature sometimes associated with mild general toxic signs, such as headache and vertigo, and mild signs of focal reaction, such as pain at the level of the lesions and increased sputum that sometimes became pink. Although it is still premature to establish a relation between these facts and the clinical form that was treated, the speakers affirm that the recrudescence is more frequent and more evident in patients with the severest evolutive forms and with toxemic conditions. One effect of the drug is the diminution, sometimes very pronounced, of expectoration in which the number of Mycobacterium tuberculosis organisms decreases or disappears in a few days, at least as is revealed by direct examination. After reporting on the general effects observed, the speakers discussed some particular cases of which they presented the radiograms showing disappearance of exudative "halos," reduction of the volume of cavities, and improvement in the efficiency of pneumothoraces. These radiograms are of great interest because up-to-date only radiographic variations of little importance have been reported. They concluded that isonicotonic acid hydrazide is a drug with an undoubted antituberculous action; however, it is still premature to evaluate its importance and limitations. Encouraging is the fact that it exerts its action on clinical forms resistant to antibiotics and also, although in a palliative way, on severe diffused ulcerous-caseous evolutive forms for which there was no therapy.

Drs. De Castro and Galassi reported observations made in the Istituto Ospedaliero of Forlí on patients with pulmonary tuberculosis treated with isonicotinic acid hydrazide. They emphasized the efficacy of the drug in some patients with pluricavitary tuberculosis; these patients have been followed up for seven weeks only. Some results of laboratory investigations and especially some blood findings are of great interest. Dr. Sega called attention to a particular aspect of acute miliary tuberculosis that he observed after isonicotinic acid hydrazide therapy. Contrary to the results reported by others he did not see any improvement in patients with this disease. He did not know whether to attribute this failure to a delayed action of the drug or to particular conditions of the Myco. tuberculosis.

Professor Fontana stressed that the proper dosage of the drug should be established. He recalled how the history of antibiotic therapy is dominated by changes in dosage (sulfonamides, penicillin, and streptomycin). Therefore, eventually surprises may come from the therapeutic experience with isonicotinic acid hydrazide. From his point of view the diffusibility of the drug pointed out by Professor D'Arcangelo and others is a very good property; it may be that its permeability through the meninges is due to the pyridinic ring that is present in the hydrazide and that makes the drug analogous to sulfamido-pyridine, which also diffuses well through the meninges. It is hard to establish how much of the therapeutic action of this drug is attributable to its

bacteriostatic and to its bacteriolytic power and how much to the stimulus of the tissue defense powers. The decrease in leukocytosis that was reported by Professor D'Arcangelo may be due to the influence of isonicotinic acid hydrazide on secondary infections in patients with severe ulcerous forms of tuberculosis. In fact, the tuberculous infection alone does not alter greatly the number of leukocytes.

LONDON

Importation of New Drugs.—The procedure governing the importation of new drugs into Great Britain from the United States causes considerable confusion on both sides of the Atlantic. In a lecture, which was recently published in the *British Medical Journal*, (2:385, 1952) Sir Weldon Dalrymple-Champneys, deputy chief medical officer, Ministry of Health, who is largely responsible for this branch of the ministry's activities, has outlined the present position. The government departments primarily concerned with the importation of drugs are His Majesty's Customs and Excise and the Board of Trade, but they depend on the Ministry of Health for expert advice whenever medical remedies are involved. This applies particularly to "therapeutic substances" as defined by the Therapeutic Substances Act of 1925, i. e., substances "the purity or potency of which cannot be adequately tested by chemical means." Such substances include insulin, penicillin, and blood products. Difficulties arise with preparations that are not covered by this act "either because they are of a kind to which the Act does not apply or because they are not mentioned, either individually or generically, in the Schedule to the Act. In such cases," Sir Weldon comments, "we have to consider whether the substance should be added to the Schedule if suitable, and whether on medical grounds we can recommend its admission to this country. Such advice is often difficult to give. For example, the antibiotics are being developed in a continuous stream, mostly in the United States, and the issue of each new one is accompanied by glowing claims for its effectiveness in a number of different infections. But we have to determine, in the first place, whether it is worthy of serious attention, and whether it is of sufficient importance to merit all the labour involved in devising a schedule to the Therapeutic Substances Regulations. . . . Even when we decide we must take it seriously it may still be a long time before satisfactory tests . . . can be devised to safeguard the patient."

In commenting on applications for permission to import a new remedy for research purposes, he said: "Obviously our pharmaceutical manufacturers, some of whom maintain research establishments of very high class, should not be hampered in their investigation of new remedies from abroad (on which they may often improve), but it must be remembered that 'research' may mean something very far short of scientific investigation, and that the free distribution of new remedies to doctors is a well-established method of 'creating a market,' the customers in which may not be as discriminating as we would wish. The foreign manufacturers, moreover, well know that the new remedy, on the development of which they have perhaps spent vast sums of money, may be superseded in a short time by a superior rival, so they have got to recoup themselves as quickly as possible."

The lecturer noted that in 1951 Great Britain spent over $187,000 on cortisone and over $582,000 on corticotropin and this year the expenditure will be greater. On the question of free gifts of drugs Sir Weldon remarked, using cortisone as an illustration: "The importation of free gifts of medical remedies is usually permitted, though H. M. Customs can forbid it if they choose. Many kind persons in the United States, both medical and lay, have sent free gifts of cortisone to doctors here for use in particular cases, or direct to the patients themselves, and you may reasonably ask, 'Why not?' Well, there is one very important consideration in such cases, apart from the danger of administration to the patient without proper control—namely, the starting of a treatment which cannot be maintained. I have received many, and often pathetic, appeals for cortisone for the treatment of patients with rheumatoid arthritis who have been greatly benefited by the injection of 'free gift cortisone,' the supply of which has failed. Usually I have been forced to refuse the request, though I knew that the last state of the patient would be worse than the first, because our limited supplies of cortisone—all that the manufacturers have been able to let us have—must, in fairness to the general body of patients and in order to obtain reliable information about its best method of use, be distributed to the 56 centres now holding it, where there are experienced physicians and adequate laboratory facilities. And what of applications to import cortisone against dollar payments? Well, there are two cogent objections to allowing such applications. The first is that this means 'jumping the queue,' and that it would be unfair in principle for patients to obtain a remedy merely because they could pay for it, in preference to others whose needs are as great or perhaps greater. The second objection arises from the fact that in the United States cortisone is obtainable only on prescription—that is, for the treatment of an individual patient in America—so that any cortisone bought by private individuals in this country is obviously 'black market.'"

Levy on Prescriptions.—On June 1 the regulations imposing a levy of 1s. per prescription form issued under the National Health Service and payable by the patient came into force. The Ministry of Health has issued a comparative analysis of the number of prescriptions issued during June, 1952, and June, 1951. This shows that the number of prescriptions submitted during June, 1952, was 14,416,800, which represents a decrease of 15.57% compared with June, 1951. The number of prescription forms submitted in June, 1952, was 8,545,000, which represents a decrease of 20.4%, compared with June, 1951. The average number of prescriptions per form was 1.69 in June, 1952, compared with 1.57 in June, 1951. The proportionately greater decrease in the number of prescription forms is due to a larger number of prescriptions per form, a tendency which was expected, as the levy is 1s. per form, not per prescription, and there is no restriction on the number of prescriptions that a physicians can write on one form. These findings are in agreement with a sample survey reported on by the *Pharmaceutical Journal*. It is too early to draw any conclusions, but it does look as if the imposition of the levy resulted in a decrease in the national expenditure on prescriptions. An interesting feature of the *Pharmaceutical Journal* investigation is the position in the teaching hospitals: "It seems that only a few patients have grumbled. . . . Patients appear to regard the payment as not unreasonable; perhaps some of them remember a similar charge made for medicines in the former voluntary hospitals, where a flat rate was payable at the dispensary and all other treatment of outpatients was free."

The annual report of the executive council of the city of Sheffield for the year ended March 31, 1952, shows the same trend in dental and ophthalmic appliances, since a similar charge for them was imposed a year ago under the National Health Service. The payments for dental treatment were £509,000 in the year ending March, 1950, £499,000 in the following year, and £340,000 in the year covered by the current report: a reduction of approximately one-third compared with two years ago. The number of sight tests carried out fell from 57,401 in the year ended March, 1951, to 39,768 in the current year: a reduction of 31%.

Miners' Nystagmus.—In an address to the North of England Institute of Mining and Mechanical Engineers, Prof. R. C. Browne, of the Nuffield Department of Industrial Health, King's College, Newcastle-upon-Tyne, described experimental work with kittens that seemed to suggest that lack of light was the fundamental factor responsible for miners' nystagmus. In one experiment, for instance, in four out of six kittens, rotary nystagmus developed after the animals were kept in the dark for four to seven weeks. Three of the affected kittens recovered in a week after being returned to daylight. The importance of this investigation lay in the fact that it showed that darkness could produce nystagmus in animals with a visual apparatus similar to that of man. One of the unfortunate consequences of the present difference of opinion as to the cause of miners' nystagmus is that both physicians and mine managers tend to label miners with nystagmus as neurotics, while both the victim and his colleagues consider that this condition means the end of the victim's useful working life.

CORRESPONDENCE

GROUP PRACTICE WITH SPECIAL REFERENCE TO OBSTETRICS AND GYNECOLOGY

To the Editor:—Group clinic practice is under consideration at present by many physicians in this country. Numerous articles have been published on the subject, but we feel that there should be more recorded experience with this type of clinic practice from the practitioners themselves.

Our clinic is located in Texarkana, which has a population of 50,000, and can be classified as a medical group family practice clinic. We organized in 1946, with a general surgeon, obstetrician-gynecologist, and internist. At present, we have seven physicians and the following departments: general surgery, obstetrics and gynecology, internal medicine, pediatrics, general practice, and industrial surgery. We get some physician referrals locally and from the surrounding communities, but we operate chiefly as an interdepartmental referral clinic type of unit.

A practice of this type means that each clinic partner, regardless of the specialty, will assume the role of family physician for those families that have used him in some capacity and like him as a doctor. He then becomes a family doctor as well as a specialist, and the family, not the doctor, makes the choice. This specialist physician, acting as a family doctor, makes for good public relations for the profession as a whole, and there is a trend today toward the encouragement of this type of practice.

The clinic partner doing obstetrics and gynecology in a medical group family practice clinic is in a better position to be the family doctor than the others, because for some reason the mother always feels that the doctor who delivered the baby ought to be consulted first when the child later has an illness or accident. This obstetrics and gynecology partner has some disadvantages also in that there are usually fewer physician referrals to his department owing to the fact that most cities of this size have many established general practitioners with wide experience in obstetrics. Then, too, there is a tendency on the part of the general surgeons to operate on their own gynecologic patients. It can be said that the only general surgeons in Texarkana who do not perform their gynecologic surgery are those who belong to one of the three local group clinics. One of the distinct advantages that the obstetrics and gynecology partner has in this type of clinic is the fact that the obstetrics and gynecology practice is forced to increase as the other departmental practices grow.

In the medical group family practice, the house visits have to be made by the clinic partner who is looked on by that particular family as the family doctor. Of course, this physician, when called out, will render whatever emergency treatment is necessary and refer the patient to the proper partner. When hospitalization is necessary, he will admit the patient to the hospital and assume the responsibility of locating the partner who will in turn treat the patient. If the patient should require general surgery, it will be necessary in most instances for the obstetrics and gynecology partner or the general practice partner to act as assistant to the general surgeon. By the same token, the general surgeon or the general practice partner acts as assistant to the obstetrician and gynecologist in cases requiring obstetric and gynecologic surgery. If the clinic has grown to a size that would justify having two partners in each of the departments, then, of course, such an arrangement would not be necessary. The general practice partner not only would assist in surgery and obstetrics and gynecology but also would act as surgeon or as the obstetrician and gynecologist in certain cases in which he is qualified to do so.

Emergency cases are handled at both of our local hospitals by the staff members, who rotate alphabetically on the roster, regardless of their specialty. If the physician on emergency call happens to be the obstetrics and gynecology partner, he will render first aid treatment and then call the designated doctor, depending, of course, into which specialty the case falls. Often the emergency call will be an obstetric or gynecologic problem, and, of course, he is responsible for the definitive treatment of this patient.

Dr. Walter A. Ruch, in the chairman's address to the section on obstetrics at the 45th annual meeting of the Southern Medical Association at Dallas, in 1951 (*South. M. J.* **45**:190 [March] 1952) devoted considerable time to a discussion of the treatment of atomic bomb casualties. He implied that there was a tendency on the part of many obstetricians and gynecologists to become overspecialized, so that, in times of national emergency they would not be sufficiently familiar with the many types of medical service required. The obstetrics and gynecology partner in the Texarkana plan of medical group family practice, as we have described it here, would certainly not fall into the category of overspecialization, and in a national emergency would be cognizant of all types of medical practice.

When possible, it is well for the obstetrics and gynecology partner in a clinic such as we have described to take an active interest in the teaching program at the school of medicine of his state university. Through the professor and head of the department, clinic appointments may be arranged during the school year. He should also take an active interest in postgraduate instruction and attend the university postgraduate conferences as well as take part in the various discussions. Selected obstetrics and gynecology residents could join clinics of this type in a junior partner or preceptorship capacity at first and later become associate partners. By doing this, the young doctor would have the advantage of not going through the so-called starvation period and the clinic would have the advantage of normal, healthy growth.

Our experience has been that new partners joining the clinic tend to be more satisfied working on a percentage basis than on a salary. After one to three years, depending on the incoming partner's experience and training, he should be able to qualify as an equal sharing partner.

There have been other plans of medical group practice suggested for the obstetrician and gynecologist. Dr. R. A. Bartholomew in 1942 suggested that a group of four obstetricians could share in the treatment of each patient during the period of pregnancy and delivery, one of them being available for call at all times (*Am. J. Obst. & Gynec.* **44**:553 [Oct.] 1942). Many types of partnership practice in obstetrics are in operation. These partnerships are usually located in the larger cities, however, and the practice is mostly limited to obstetrics. In many of these groups a good portion of the patients are referred from general surgeons to whom in turn the gynecologic surgery cases are referred. This is the type of practice that is largely responsible for the present clamor among the general surgeons for a separate certifying board in gynecologic surgery.

McClusky (*Med. Econ.* **24**:75 [Dec.] 1946) made a study based on an analysis of 85 groups in the United States and described "a composite group that would consist of seven physicians. It would be located in the Midwest in a city of about 60,000 population. Organized as a formal partnership, each partner would receive an equal share of the group's income. Each would have a daily average of 20 patients who would pay on a fee-for-service basis. The group would be about twenty years old, have a building of its own, a plant investment of more than $70,000 and an annual overhead of about 35 per cent."

The recently organized American Association of Medical Clinics has as its chief aims: (1) to boost standards of practice in private group clinics, (2) to foster and improve graduate medical education in such clinics, (3) to promote clinical research work, and (4) to encourage an interchange of group practice ideas and experience. A clinic to be eligible must have seven or more full-time physicians representing five different major specialties (*Med. Econ.* **27**:152 [March] 1950). These requirements differ from those defined by the American Medical Association in 1940 (Bureau of Medical Economics: Group Medical Practice, Chicago, American Medical Association, 1940) which specified that there must be at least three physician members

and that the receipts from medical practice must have been pooled in some manner and then redistributed to members according to some previously arranged plan.

It is obvious that a beginning group in a city of 50,000 or less population would have some difficulty in organizing with more than three physicians. In Texarkana, we have three group clinics in operation, and each of these groups started with three doctors. At present, we have approximately the same number of physicians affiliated with the medical groups as there are in nongroup practice here.

We find it not too difficult to visualize a situation in which the American Medical Association or the American College of Surgeons might see fit some time in the future to classify and standardize all group clinics just as they did the various types of cancer clinics. Along with this program of classification and standardization would be the difficult job of establishing minimum training requirements for the various clinic partners, including the partner practicing obstetrics and gynecology.

W. B. HARRELL, M.D.
Daniel-Harrell Clinic
Medical Arts Building
Texarkana, Texas.

IRRADIATION AND STERILITY

To the Editor:—The paper by I. C. Rubin entitled "Third Generation Follow-up in Woman Receiving Pelvic Irradiation," which appeared in THE JOURNAL (**150:**207 [Sept. 20] 1952) and was described under the heading "X-ray Doses Do Not Harm Future Children" in *Science News Letter* (**62:**213 [Oct. 4] 1952), may lead some clinicians to the view that there are no genetic hazards of x-irradiation in man. The opinion of this writer, and presumably of every geneticist, is that such a conclusion is not justified. Dr. Rubin does not actually state that there is no hazard, but he believes his own cases and those of others fail to support the claim that there is one. It seems necessary, therefore, to examine in detail the cogency of Dr. Rubin's negative evidence and the validity of his arguments.

Dr. Rubin's material consists of one child, "normal by all pediatric standards," born on Oct. 4, 1951, who is the grandchild of a woman who had suffered from habitual amenorrhea and whose ovaries had been given a "stimulating" x-ray treatment on Dec. 5 and 16, 1923. A son, the father of the grandchild, was conceived after this treatment and was born on Oct. 7, 1924.

Dr. Rubin attaches special significance to the fact that he is dealing with the grandchild of a woman who received irradiation. He writes that his case "has an important bearing" on the question of whether x-rays produce mutations in humans, and he cites four similar cases of grandchildren reported by Kaplan. However, the effects of dominant mutations and sex-linked recessives could be detected more efficiently by studying the children, rather than the grandchildren, of irradiated women. Also, the detection of new autosomal recessive mutations requires at least one more generation and would be possible then only following the mating of sibs, half sibs, or parent and offspring.

A far more important point about Dr. Rubin's material is that it is inadequate for the drawing of general conclusions about genetic hazards. The measurement of genetic effects in man is extremely difficult. One has only to imagine the careful, extended and extensive observation that would be required to detect effects as great as, say, 25% shortening of the life span to realize the difficulty. A simple example of the difficulty is apparent in Dr. Rubin's paper, where mention is made of two minor abnormalities in the son of the woman who had received irradiation. Dr. Rubin does not raise the question of whether these might have been caused by radiation-induced genetic changes, but it certainly cannot be proved that they were not.

The arguments used by Dr. Rubin to reinforce the conclusion he reaches from his material are comprised of four grounds on which deductions from radiation-induced genetic injury in Drosophila would seem to him "untenable for the human female." Postponing, for a moment, Dr. Rubin's first and fourth grounds for rejecting evidence from Drosophila, his third point seems to be that the effect of irradiation on fertilized eggs of Drosophila must not be compared with the mutational effects produced by irradiating the human ovary. Geneticists are not guilty of this error. Yet, in his second point, Dr. Rubin himself makes this mistake in his comparison of x-ray doses in Drosophila and women. Dr. Rubin nowhere mentions any Drosophila results other than those produced by irradiating fertilized eggs, which he describes in detail. Thus, there is no discussion of the pertinent information on germinal mutations in Drosophila.

The main object of this letter, however, is to point out that Dr. Rubin has failed to mention the extensive work on x-ray-induced mutations in laboratory mammals. The production by x-rays of dominant lethal mutations in rabbits was observed as early as 1908, by Regaud and Dubreuil, although the nature of the mutations was not recognized until after the early work on Drosophila. During the 1930's the work of Strandskov on guinea pigs and of Snell, Hertwig, Brenneke, and others on mice and rats established the x-ray induction of dominant lethals, dominant sterility, and dominant partial sterility. There was also some indication of the occurrence of dominant subvitals. Dominant and recessive point mutations in the mouse have since been obtained by x-rays, recently on a quantitative scale at this laboratory (X-Ray Induced Mutations in Mice, Cold Spring Harbor Symposia on Quantitative Biology **16:**327-336, 1951). Since Dr. Rubin has argued that Drosophila results are not applicable to man, it is interesting to see how the Drosophila results compare with the data obtained on laboratory mammals. It has been found that, for all types of mutations on which there is adequate information, the rate of induction, per gamete, for a given dose of x-rays is considerably higher in mammals than it is in the fruit fly. For the type of mutations studied in our work, the rate of induction, per locus, is also considerably higher. Thus, the observed difference between Drosophila and mammals is cause for greater caution in the use of irradiation in man than had been indicated by the Drosophila results alone.

Dr. Rubin claims that it is a "basic fallacy" to compare whole-body irradiation of Drosophila with partial-body irradiation of the ovarian region in women. All genetic experience indicates that it is only the irradiation received by the gonads, or the germ cells, that is important. Most of the work on mammals has been done with partial-body irradiation. When similar experiments have been made with whole-body irradiation, no detectable difference in genetic effects has been found.

Dr. Rubin's final point is the difference between Drosophila and man in the length of generation. Geneticists have raised this question before, not as Dr. Rubin has, with the vague assumption that, in some unspecified way, genetic effects "would have been dissipated over the years" from grandmother to grandchild, but with the possibility in mind that germinal selection might operate in gametogenesis against cells carrying mutations and that this might be more effective in longer-lived species. In our work referred to above, this possibility was explored for irradiated spermatogonia. No such effect was found for the mutations studied. Further investigation of this problem is being made. For chromosomal aberrations of certain types, of course, it has long been known, from Hertwig's work on the mouse, that there is a marked difference in the results obtained from irradiated sperm and irradiated spermatogonia.

There is one other statement in Dr. Rubin's paper that cannot be accepted. There is not the slightest justification for his belief that from a mere examination of the spermatozoa he could assure a patient of no greater risk of abnormality in his children than that taken by any would-be parent whose antecedents had never been exposed to x-ray treatment of the gonads.

At the present time we do not have, even in laboratory mammals, accurate information on the total damage to be expected in the offspring from dominant mutations induced by x-irradiation of the gonads of the mother or father. Recent work in Drosophila by Stern, Muller, and others, showing that recessive lethals commonly have deleterious dominant effects, indicates that this risk must be explored further and measured as accurately as possible. It seems likely that most of the damage will be expressed not as startling monstrosities but as subtle effects on viability. In man, we can be sure there is a risk, but we do not know its magnitude. The reporting of isolated cases of children, or grandchildren, normal at birth adds only a little to the measurement of the risk. Careful statistical studies of large numbers of persons are needed, and the cases should be followed through postnatal life. We can expect some information on the general magnitude of the damage from the work of the Atomic Bomb Casualty Commission in Japan.

In conclusion, it should be emphasized that we have dealt only with the risk of damage from induced mutations in heterozygous or hemizygous condition, of which there is some possibility of measurement in man in the foreseeable future. Estimation of the damage from mutations in homozygous condition will have to rest on the results from experimental animals.

W. L. Russell
Biology Division
Oak Ridge National Laboratory
Oak Ridge, Tenn.

To the Editor:—The report of Dr. I. C. Rubin ("Third Generation Follow-Up in Woman Receiving Pelvic Irradiation") in The Journal, Sept. 20, 1952, page 207, adds an interesting bit of information to the complex problem of the effect of ionizing radiation on women and their progeny. It is our feeling, however, that insufficient data have yet been obtained to permit the optimistic conclusions drawn by Dr. Rubin. With regard to his comments concerning the irradiation of the pregnant uterus, it is important to point out that not only the x-ray dosage but also the time in the development of the embryo at which the irradiation is received is important, as pointed out by the work of Hicks, Liane Russell, and many others. The effects of irradiation on the embryo and fetus are the result of a direct effect on growing tissues, not a genetic effect, of course.

It is true that one cannot apply fruit fly irradiation genetic experiments directly to humans, and the same applies to more recent data obtained in several laboratories on the effects of radiation on the genes of mice. Extremely small doses of ionizing radiations are capable of causing genetic changes in mice. It is a principle well established in medicine that agents harmful to laboratory animals must be assumed to be harmful to man until definitely proved otherwise. Although Dr. Rubin's observations are a valuable contribution, one cannot scientifically accept three single cases as excluding radiation effects on human genes. In animal experiments, large numbers of animals must be used to detect genetic changes after irradiation because of the very nature of genetic characteristics. Often genetic changes caused by irradiation do not appear for several generations, and, like normal genetic characteristics, do not appear in all individuals.

The immediate direct effects of ionizing radiations are always damaging, ranging from very slight alterations in chemical enzyme systems and fine changes in cell nucleus structure to actual necrosis of cells. Any "stimulating" effect is always a reaction to the injurious effect.

There should be no relaxation of caution and conservatism by physicians in administering ionizing radiation to any patient and particularly to women before the menopause.

Shields Warren, M.D.
Samuel P. Hicks, M.D.
Laboratory of Pathology
New England Deaconess Hospital
195 Pilgrim Rd.
Boston 15

To the Editor:—In the Sept. 20, 1952, issue of The Journal, page 207, Dr. I. C. Rubin reported on the follow-up of a grandchild of a woman treated by irradiation for sterility. In this article he mentions "This is the fifth such case reported; Kaplan has encountered four others." Unfortunately, the reference to these cases was not given. In the *Archives of Pediatrics* (**67**:569-572 [Dec.] 1950), I published, under the title "Do Children Born of Offspring of Mothers Irradiated for Sterility Show Abnormal Genetic Effect?" the detailed history of three of these cases described by Dr. Rubin. I am now able to report on several more children born to the daughters of irradiated grandmothers. These reports will appear in a subsequent publication. This supports the view of Rubin and others that low dose x-ray irradiation to the ovaries and pituitary as used for the treatment of female sterility produces no harmful effects in human reproduction.

Ira I. Kaplan, M.D.
755 Park Ave.
New York 21

To the Editor:—In The Journal, Sept. 20, 1952, page 207, Dr. I. C. Rubin reports the case of a woman who was given about 80 r to the ovaries and soon after became pregnant. Her child, grown to manhood, has now fathered a normal baby. Rubin argues at length to refute a widespread belief that irradiation of ovaries threatens the health of the race. He is impressed by differences in size and in the life cycle between man and the experimental animal that has yielded the largest volume of genetic evidence in regard to hereditary injuries (Drosophila). He reveals in this a failure to understand the evidence and the arguments on which our apprehensions are based.

In insects, spontaneous mutations occur, and these are inherited. Some are recessive, i. e., do not show unless mated to a similar defect. The mutation rate is increased by irradiation, more by large doses than by small ones. There is no threshold demonstrated—no dose below which no effect occurs. There is no recovery; that is to say, the effects of repeated small doses add together, even though there is a long time between doses.

As Rubin points out, human generations come too slowly to permit observations in humans to give us an answer for human heredity. We can only infer from what happens in insects and small mammals, but we have a deep conviction of the basic similarity of cytological processes throughout the animal and the vegetable kingdoms. We think the mechanisms of heredity are essentially the same for man and insect.

In view of the absence of a critical dose level and of any recovery from the injuries that produce mutations, it seems clear that the considerations of dosage, size of body, tissue overlay, and passage of time are beside the question. In view of the existence of recessive mutations the appearance of normal offspring is not completely reassuring. There is a good chance that the apprehensions of the geneticists are well founded. It could be that every irradiation of ovary or testicle that is followed by the birth of viable offspring has a chance to add to the pool of undesirable genetic factors that the race is carrying. If so, 500 r given to one person is no worse than 5 r given to each of 100 persons. It is true that the cosmic rays give each of us about one roentgen every 10 years or so. We cannot deny that they continually add to the unwanted genetic traits that the race has to carry. We do not have a period of adult haploid homozygosity, like Paramecium, which allows bad recessive traits to come to light and kill the individuals carrying them. We have to await chance matings to reveal the recessives. Consequently, the human genetic pool clarifies itself but slowly. It seems most unwise to dump any extra misfits into it.

R. R. Newell, M.D.
Stanford University School of Medicine
Clay and Webster Streets
San Francisco 15.

ACUTE URINARY RETENTION IN PREGNANCY

To the Editor:—We are taking this opportunity to answer the criticism of Dr. Rudolph W. Holmes (*J. A. M. A.* **150:**428 [Sept. 27] 1952) concerning our article "Acute Urinary Retention as a Complication of Pregnancy" (*J. A. M. A.* **149:**1011 [July 12] 1952). His statement that urinary retention as a complication of an incarcerated retroverted uterus was a relatively common occurrence in the past is not true for these reasons: First, we were able to find only three cases in all the literature besides our own. Second, a review of the obstetrical records for 35 years of a large municipal hospital in New York failed to reveal a single case. Lastly, discussion of this complication with our obstetrical colleagues reveals that they have never seen this complication among their large number of obstetrical patients.

There may be overflow incontinence in cases of retroverted pregnant uterus, as in any case of urinary retention, if the hydrostatic pressure in the bladder becomes great enough to cause the urine to escape. Our patient and those reported on in the literature, however, did not have overflow incontinence.

As to treatment, we wish to stress that intermittent catheterization is too traumatizing and inadequate. In fact, it failed in our patient before she was admitted to the hospital. As stated in our article, continuous catheter drainage, with administration

of sulfonamides and antibiotics for at least five days, is necessary if the bladder musculature is to recover and acute urinary infection and urinary sepsis are to be avoided. This may have to be repeated until the uterus releases itself, usually during the fifth month, or until it can be replaced manually.

Although we did not advocate it in our article, it was formerly thought that rapid evacuation of the chronically distended bladder accounted for the high incidence of vesical and renal hemorrhage, oliguria, anuria, or even death in cases in which it was employed. Studies by Hryntschak (1948), Creevy (1932), Breecher and Chwalla (1931), and Seifert (1940) in hundreds of patients with distended bladders have shown that infection is a more dominant factor than rapid evacuation in causing complications. Creevy found that in all but 5 of 70 patients who died after catheterization in the presence of residual urine, death was caused by renal infection. The employment of sulfonamides and antibiotic therapy has reduced the sequelae following sudden decompression, proving the importance of infection in the process that was formerly so often fatal.

Jesse J. Hymes, M.D.
Maxwell Spring, M.D.
30 E. 40 St.
New York 16.

ILEOSTOMY CLUBS

To the Editor:—The communication concerning an ileostomy club by A. S. Lyons in the Oct. 25 issue of The Journal, page 812, will, in my opinion, encourage more colectomies for chronic ulcerative colitis. This is psychotherapy in reverse. Instead of minimizing the handicap, such a proposal directs more attention to it by throwing the patient into an "ileostomy environment" so to speak. "Ileostomy friends" are not desirable contacts for ileostomy patients. Although such intentions may be laudable, I fear that this is an admission of failure of physicians to cope with the problems of chronic ulcerative colitis and demonstrates their impatience in the handling of this distressing disease. The ideal treatment of chronic ulcerative colitis is not colectomy and permanent ileostomy. The latter procedure is indicated only in the rare and severe complications of chronic ulcerative colitis. Let us not regard our failures as successes! A colectomy for chronic ulcerative colitis is indicative of poor medical management prior to surgical intervention.

Dr. Lyons hopes that others will follow his example and organize ileostomy clubs. I can say only that this will give publicity to a radical procedure of which neither the patient nor the surgeon should be proud. Let us rather mobilize all our available knowledge for the early and prompt medical treatment of chronic ulcerative colitis. An ileostomy for such a patient is something to hide and not to organize clubs with. A permanent ileostomy performed by a surgeon as a treatment for chronic ulcerative colitis in the absence of serious complications indicates that poor medical care may have prevailed.

William Z. Fradkin, M.D.
27 Prospect Park West
Brooklyn 15, N. Y.

GASTRIC HODGKIN'S DISEASE

To the Editor:—In a clinical note in The Journal, Aug. 16, page 1460, Morris reported a case of gastric Hodgkin's disease and discussed the symptoms and diagnosis, stating, as is well known, that "there are no diagnostic symptoms." In his conclusions he remarked the "Roentgen findings may be quite indicative [of lymphoma]," although he had mentioned earlier that "the roentgenographic findings have usually been interpreted as being indicative of carcinoma and, less frequently, of ulcer." In my experience with proved gastric lymphoma, the roentgenologists have often described very thick gastric rugae but have been unable to differentiate severe gastritis, infiltrating carcinoma, and lymphoma.

The purpose of this communication is to emphasize the fact (not mentioned by Morris) that gastroscopy with biopsy by means of the Benedict flexible operating gastroscope is a positive method of differentiating gastritis, infiltrating carcinoma, and lymphoma. Although there are about 200 biopsy gastroscopes in general use and favorable reports on its use have been published by Shallenberger, Wirts, and Wiebenga, there seems to be too little recognition of the fact that gastroscopy has at last come into its own with the other endoscopic techniques by permitting an exact gastric diagnosis by gastroscopic biopsy under direct vision.

Edward B. Benedict, M.D.
Department of Surgery
Massachusetts General Hospital
Boston 14

MISCELLANY

OCCUPATIONAL HAZARDS IN MICROBIOLOGY

On the basis of past experience it is estimated that during the coming year approximately 65 laboratory workers in the United States will become ill as a result of infection acquired in laboratories concerned with various aspects of microbiology. One or two of these may die.

The Peruvian medical student Carrión died of Oroya fever in 1886 after inoculating himself with the blood of a patient suffering from verruga in an attempt to learn more about the latter disease. Unexpectedly, his drastic experiment showed that the two diseases were due to the same agent, now known as Bartonella bacilliformis. Since Kolletschka, associate of Semmelweis, contracted fatal septicemia while performing an autopsy on a woman dead of childbed fever, numerous physicians have acquired infections, some fatal, while performing postmortem examinations. The dramatic experiments of the Walter Reed Commission at the beginning of the present century resulted in the transmission of yellow fever to Carroll and Dean, who voluntarily exposed themselves to the bites of mosquitoes that had previously bitten patients with yellow fever. They recovered, but Lazear, who was bitten accidentally, died of yellow fever. More than 25 years later this same disease was responsible for the deaths of Stokes, Guilett, Noguchi, and Young, who went to Africa to seek the disease agent transmitted by the mosquito. Because of the development of effective immunization and improvement in techniques, those who have worked with the yellow fever virus in recent years have been protected from the risks taken by their predecessors.

Rickettsial diseases have also taken their toll. The American investigator Ricketts, for whom the micro-organisms were named, died of typhus fever while studying that disease in Mexico in 1910. Ricketts had previously shown that wood ticks transmitted Rocky Mountain spotted fever, a rickettsial disease which, in the years from 1921 to 1927, was to cause the death of McClintic, Gettinger, Cowan, and Kerlee. Bacot, likewise, while studying the infectivity of louse excreta in Egypt in 1922, contracted fatal typhus fever.

Between 1905 and 1918 other fatal laboratory-acquired infections were recorded in the case of relapsing fever, undulant fever, plague, glanders, and meningitis. Eventually certain disease agents came to be recognized as being especially hazardous to the microbiologist. The virus of psittacosis caused infection in 44% of the personnel of a research laboratory at the National Institutes of Health in 1930. The 74 known instances of brucellosis among laboratory workers were summarized in 1941, and a number of additional cases have occurred since that time. Reported instances of laboratory-acquired typhoid, tularemia, Q fever, and coccidioidomycosis indicated that the agents of these diseases were among those most likely to infect those studying them. In 1949 Sulkin and Pike collected records of laboratory infections caused by viruses alone and found 222 cases, of which 21 had terminated fatally.

Some microbiologists spend a lifetime in the laboratory without contracting any of the diseases they study; others are less

Condensed from *The Scientific Monthly*, October, 1952. The authors are R. M. Pike, Professor of Bacteriology, Southwestern Medical School of the University of Texas at Dallas, and S. E. Sulkin, Professor and Chairman of the Department.

fortunate and become infected more than once. The all-time record is held by Edward Francis, eminent investigator at the National Institutes of Health, who during a period of 27 years contracted dengue, tularemia, undulant fever, psittacosis, and relapsing fever as a result of his laboratory work. Two other bacteriologists who have worked at the same institution—George McCoy and Charles Armstrong—have each had three laboratory-acquired diseases, and others, too numerous to mention, are known to have acquired more than one.

When a new disease agent is discovered, there is a good chance that it will infect some of the investigators who study it in the laboratory. Only recently that has happened with Rickettsia akari, the cause of rickettsialpox, which was first recognized in New York City in 1946. Already there have been four cases of rickettsialpox acquired in the laboratory. The most recent additions to the virus group, the Coxsackie viruses, were first described in 1948. Although their relation to human disease is not yet completely understood, on at least six occasions they have infected the persons working with them.

Sometimes an infection acquired by a laboratory worker is the first instance of that disease known to occur. Thus, the name of the young investigator Brebner is associated with the "B virus" infection from which he died in New York City in 1932. His illness followed the bite of a laboratory monkey that was to be used in research in poliomyelitis. Since then only two other B virus infections have been recorded, both contracted from laboratory monkeys. The virus that causes louping ill, an encephalomyelitis of sheep, was discovered in 1930. Within a few years six laboratory workers contracted the disease, but it was not until 1948 that the first human infection caused by this virus was recognized outside the laboratory. Q fever was first observed in Australia, but the Rickettsia that causes it was first isolated in the United States, from ticks at the Rocky Mountain Laboratory of the Public Health Service, in 1938. After visiting this laboratory, Rolla Dyer, then of the Public Health Service, contracted Q fever. His infection was the first recognized case in this country. More than 60 cases of Q fever that were due to laboratory-propagated strains of this micro-organism had occurred in the United States before the disease was found to occur naturally among packing house workers.

As the science of microbiology expanded, more and more persons became engaged in work that required close contact with the agents of infectious disease. The risk of infection was experienced not only by those looking for previously unrecognized causes of disease but also by technicians performing routine examinations in clinical and public health laboratories, by animal caretakers, and by those concerned with cleaning laboratory apparatus. Unless some unusual circumstances were involved, instances of laboratory infection were no longer reported in the medical literature; consequently, there was no way of knowing how frequently laboratory infections were occurring, what types of work were most dangerous, or where the greatest efforts should be made to establish safety measures. One way of gaining more complete information regarding the occurrence of laboratory infections was to question as many laboratories as possible. To this end the National Medical Advisory Council requested that a survey be made. This was done in 1950 by Sulkin and Pike under the sponsorship of the National Institutes of Health. Nearly 5,000 laboratories in the United States were asked about infections that had occurred during the previous 20 years. From the data thus assembled—although they were necessarily incomplete—information was obtained regarding 1,334 cases of infection arising presumably in the laboratory.

All kinds of infectious disease agents were represented in these illnesses, although some were more frequently involved than others. Deaths occurred in all categories except in those due to parasites. The frequency with which the various kinds of agents were involved, however, is not necessarily a reflection of the risk involved in working with them. One important contributing factor to this distribution is the number of persons under risk. For example, a larger number of workers in a greater variety of laboratories are exposed to various kinds of pathogenic bacteria than to viruses or Rickettsia. On the other hand, a greater proportion of viral and rickettsial infections have been fatal.

Tuberculosis, which ranks second among the bacterial diseases presumed to be of laboratory origin, has been a matter of special concern because of the large numbers of persons who handle tuberculous materials in clinical, research, and teaching institutions and because of the severity and prolonged course of the disease. The potential hazard of tuberculosis is considered so great that several medical schools no longer permit classes to study materials containing living tubercle bacilli.

Laboratory infections are not confined to the scientific personnel most closely associated with the infectious agents. Although professional and technical workers, research assistants, and graduate students experienced about three-fourths of the illnesses, office workers, janitors, and dishwashers became infected as a result of activities in the laboratories with which they were associated. Students were infrequently involved, although the number in courses dealing with infectious disease is estimated to be greater than the number of persons in any other group concerned.

The circumstances leading to cases of infectious hepatitis (jaundice) in the laboratory are unique in that the material from which they arise is often obtained from apparently well persons. Attention was first attracted to this form of hepatitis when it was observed to occur in persons who had received injections of blood plasma or preparations containing serum. The virus that causes this disease may be present in the blood for several months without giving rise to symptoms, with the result that any blood specimen from an apparently healthy person may contain the virus. In the laboratory, persons who examine blood, even though their work may not be directly related to infectious disease, and those who clean the glassware containing the blood, are in danger of contracting hepatitis. In recent years more laboratory infections have been caused by this agent than by any other virus.

In only one-fifth of all laboratory infections can the source be traced to an accident. Some types of accidents tend to be repeated: Infectious material is drawn into the mouth through a pipet; the skin is accidentally pricked with a hypodermic needle or the needle may separate from the syringe during animal inoculation; or a test tube is broken or its contents are spilled. In many laboratory infections the pathway of transmission is atmospheric, although this may not be characteristic of the naturally occurring disease. This mode of transmission has accounted for at least one fatal case of typhoid. Encephalomyelitis and typhus fever have resulted repeatedly in the laboratory from inhalation of the agents of these diseases, although the naturally occurring infections are transmitted by arthropod vectors.

Recent interest in the prevention of laboratory infections has resulted in the establishment by the American Public Health Association of a committee to study the occurrence of such infections, to attempt to determine their causes, and to recommend means of eliminating the hazards that exist. As in other fields of activity, occupational hazards are being recognized in infectious disease laboratories, and steps are being taken to control them.

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

REPORT OF THE COUNCIL

The Council on Medical Education and Hospitals has authorized the following statement for publication.

DONALD G. ANDERSON, M.D., *Secretary.*

STATEMENT OF THE AMERICAN BOARD OF SURGERY REGARDING EMERGENCY MEDICAL CALL SERVICE

The American Board of Surgery has no objection to those holding its certificate being listed for emergency call service as recognized by the county medical societies throughout the country. The board wishes it made clear, however, that this action only refers to participation in such a service, as, in general, it has always been the board's policy that one who holds this certificate must limit his work to surgery.

BUREAU OF LEGAL MEDICINE AND LEGISLATION

MEDICOLEGAL ABSTRACTS

Medical Practice Acts: Constitutionality of Illinois Law.—The defendant was charged with engaging in the practice of medicine without a license and was found guilty by a jury in the trial court. From such finding she appealed to the Supreme Court of Illinois.

The defendant was a woman about 60 years old at the time of the hearing. She was a native of Sweden, had been in this country about 27 years, and was a citizen. She claimed to be a faith healer or healing minister ordained by the Central Baptist Church of Chicago and was a member of a sect that believed in and practiced divine or faith healing. The prosecuting witness went to the defendant's apartment as an investigator on behalf of the Department of Registration and Education. The defendant answered the door, and the prosecuting witness asked to see Dr. Frank Handzik. The defendant advised her that Dr. Frank Handzik was not in and asked her if she wanted a treatment, to which the prosecuting witness replied in the affirmative. The defendant then told the witness that she was Dr. E. O. Handzik and that she did the same kind of work as Dr. Frank Handzik. She invited her into the apartment. The defendant asked her where she had her pain, and the witness told her that it was between her shoulders. The defendant then told her that she had arthritis. The defendant asked her if she believed in God, and, when the witness replied that she did, the defendant requested a donation of $4.00 for her church and told the witness that she would give her a treatment and that she, too, had had arthritis and had cured herself. The witness then described the treatment given her, which consisted of rapid inhaling, exhaling, and drinking two glasses of water, one described as "holy" water and the other as "atomic" water. The defendant also went through the rapid breathing process and stated that its purpose was to make one hot and to make contact with God easier. The defendant placed her hands on the witness and prayed. The defendant told the witness that she also had machines, the "estemeter" and "vita ray" machines, and if the witness did not get relief from the treatment she would apply "hot wires." The witness also testified that the defendant gave her a printed card bearing the names of Dr. Esther O. Handzik and Dr. Frank A. Handzik; "Christian Psycho-physicians" together with the address, phone number, and office hours were printed under the names. The defendant testified that she believed in and had studied and practiced divine healing through prayer as a minister of her church. She denied charging a fee but admitted that she accepted a donation for her church and stated that this donation was usually divided, 10% for the church and 90% for her. She denied making any physical examination or diagnosis, and she denied giving the witness the card but stated that she knew such cards were in the house. She stated that she was employed as a tailor to earn her living and did not depend on any income from healing treatments for that purpose.

Section 24 of the Medical Practice Act provides, in substance, that if any person shall hold himself out to the public as being engaged in the diagnosis or treatment of human ailments or shall suggest, recommend, or prescribe any form of treatment with the intention of receiving any fee or gift, or any compensation whatever, or shall profess to heal any ailment or supposed ailment of another, or shall maintain an office for examination or treatment of any persons afflicted with any ailment, or shall attach the title Doctor, Physician, Surgeon, M.D., or any other word or abbreviation to his name, indicative that he is engaged in the treatment of human ailments as a business, and shall not then possess in full force and virtue a valid license issued by the authority of this state, he shall be guilty of a misdemeanor and on conviction shall be punished by a fine or imprisonment in the county jail or by both fine and imprisonment. Section 36 provides that all such fines shall inure to the department. Section 37 provides that the act shall not apply to certain named classes of persons, including "persons treating human ailments by prayer or spiritual means as an exercise or enjoyment of religious freedom."

The defendant first contended that section 24 above is invalid because the general language used therein is repugnant to section 37. This contention, said the Supreme Court, is untenable. It is an elementary rule of statutory construction that all the parts of an act relating to the same subject should be considered together and not each alone, so that the purpose and intent of the whole act can be ascertained and given effect as consistent provisions to accomplish the purpose intended. The provisions of section 37 merely constitute exceptions to the general provisions of section 24, and when the whole act is read together there is no inconsistency or repugnancy.

The defendant next contended that the subject matter of section 24 is not embraced or expressed in the title of the act. There is no merit in this contention, said the Supreme Court. The title should express, in general terms, the purpose of the act, and any provisions germane to that purpose may be inserted as long as they are not inconsistent with or foreign to the general subject. The title of the Medical Practice Act is "An Act to revise the law in relation to the practice of the treatment of human ailments for the better protection of the public health and to prescribe penalties for the violation hereof." Section 24, said the court, provides that the doing of certain specified acts for the purpose of treating human ailments, without a valid license, constitutes a misdemeanor and provides penalties on conviction thereof. The purpose and object of the act, as set out in the title, is to regulate the practice of treating human ailments. The specific acts prohibited by section 24 are all methods of treating human ailments.

The defendant's next contention was that the act is invalid because section 36 provides that all fines shall inure to the Department of Registration and Education instead of providing for such fines to be paid to the state or the county for public use and benefit; this, she said, is in violation of sections 16 to 20 of the state constitution. The general assembly, said the Supreme Court, has the power to impose penalties and the power to dispose of them, and section 36 of the Medical Practice Act does not violate any of the constitutional provisions relied on by the defendant.

The defendant's contention that section 24 provides punishment for any person using the titles "Doctor" and "Physician" without a valid license ignores the plain language of the statute, said the court. Not every use of the titles is punishable but only the use of the titles in an unlawful manner "indicative that he is engaged in the treatment of human ailments." The use of these titles, the court continued, is not an inherent or constitutional right in everyone, and the General Assembly may regulate their use in the treating of human ailments. It is common knowledge that these titles, in general use as applied to human ailments, have a connotation indicating special qualifications and training to diagnose and treat afflicted persons, and the misuse of such titles could cause deceptions, frauds, and practices dangerous to the public health. Laws regulating the use of these titles when health and even life itself are involved are not unreasonable or arbitrary. We think, the court concluded, that the prohibition of the use of such titles "indicative that he is engaged in the treatment of human ailments as a business" is reasonably necessary and appropriate to accomplish the legitimate objects and purposes of the Medical Practice Act and is within the police power of the state.

The defendant's contention that section 24 violates and infringes on religious freedom is likewise untenable, said the Supreme Court. As pointed out, section 24 must be read in

conjunction with section 37, and that section specifically exempts "persons treating human ailments by prayer or spiritual means as an exercise or enjoyment of religious freedom."

The defendant next contended that the trial court erred in overruling the motion for a directed verdict on the ground that all the evidence, both for the state and the defendant, showed that this was purely a case of faith healing and was an exercise of her right of religious freedom. An examination of the instructions revealed that the jury was adequately instructed in regard to the defendant's claimed exemption. The jury heard the evidence and observed the witnesses, and by its verdict found the defendant was not one of the exempted class. We cannot say, said the Supreme Court, that the evidence here, with the legitimate inferences deductible therefrom, is insufficient to support that verdict.

Finally, the defendant contended that the prosecution failed to prove that she had no license, an essential allegation of the information. As a general rule, said the Supreme Court, it is elementary that the state is required to prove every essential averment of the charge against the defendant. There usually is no burden on a defendant to disprove any averment or even to make a defense; however, the court continued, there is an exception to this rule in this type of case. In prosecutions for doing an act that the state prohibits to be done by any person except those who are duly licensed, the negative averment that the defendant had no license, being an averment peculiarly within the knowledge of the defendant, is taken as true, unless disproved by the defendant. The State was not required to prove that the defendant had no license. Furthermore, said the court, we are unable to see any unfairness or harm in applying this rule, where, as here, the defendant took the stand and testified. Accordingly, the Supreme Court held that all of the defendant's contentions on appeal were without merit, and the judgment of conviction was affirmed.—*People v. Handzik, 102 N. E. (2d) 340 (Illinois 1951).*

Hospitals: Osteopath's Right to Operate Hospital as Incident to Practice.—The plaintiff osteopath applied for a license to operate a hospital as an incident to his practice of osteopathy. His application was denied by the director of health and the denial affirmed by the district court. The plaintiff accordingly appealed to the Supreme Court of Nebraska.

Since 1931 the plaintiff had been a licensed and practicing osteopathic physician and surgeon in Nebraska. He owned, maintained, and operated a hospital in Steele City from 1935 until 1948 as an incident of, and in connection with, his practice of osteopathy. He applied for a license to operate his hospital for the year 1948, and a license therefor was granted and issued to him. His application for a license to operate the hospital for the year 1951 was denied, but he was granted and issued a license to operate a maternity hospital or home during that year. The plaintiff conducted himself properly and ethically as an osteopath strictly within the authority and limitations of his license. Any person at, or who came to, the hospital and required or desired the services of a regular physician and surgeon was furnished or permitted to have one.

The Nebraska legislature in 1947 adopted an act relating to the licensing, inspecting, and regulating of hospitals. This act made it unlawful, after Jan. 1, 1948, for anyone to maintain and operate a hospital without obtaining a license to do so. The department of health, with the advice of the hospital advisory council created by this act, was required to adopt, promulgate, and enforce standards for different types of hospitals and regulated institutions to be licensed, and was empowered to modify, amend, and rescind any standard adopted. The department of health acted, and in April, 1950, adopted standards, among which is the following: "All persons admitted to any institution covered by these standards must be under the care of a person licensed to practice medicine and surgery in Nebraska." The plaintiff has not complied with, and does not intend to satisfy, the requirement of this standard.

The department of health, for administering the act referred to, has classified hospitals as "general hospital" and "special hospital (i. e., orthopedic, contagious, etc.)" and the above standard is applicable to either class. It requires any hospitalized person to be under the care of a person authorized to practice surgery in Nebraska. Duly licensed osteopaths, under the rules promulgated by the department of health, cannot have and operate a hospital facility for the care of persons suffering from sickness, injury, or deformity who are legally and properly their patients. They may render osteopathic healing practices and services in their offices or in their homes, or at any other place in Nebraska except in a hospital. For osteopaths to have a patient in a hospital in Nebraska, the department of health demands that the patient should be cared for, while there, by a regularly licensed physician and surgeon. In fact, the literal terms of the standard are that at the very time a person is admitted to a hospital he must then be under the care of a regular physician and surgeon.

The plaintiff performs professional services for persons who have suffered sprains, fractures, and injuries that do not require operative surgery; for persons afflicted with chronic heart disorders, rheumatism, and maternity cases; and for persons with other ills and conditions that can properly be cared for by an osteopath. Many of his patients desire and require hospitalization. He is, however, unable to secure a license to furnish it to them, except maternity cases. His patients cannot enter a hospital unless they place themselves under the care of a regular physician and surgeon. The realistic view is that an osteopath cannot have a patient in a Nebraska hospital unless the patient is a maternity case. He is, therefore, denied an advantage and right to which he is entitled by, and as an incident of, the authority granted to him by the state to practice osteopathy. The standard adopted by the department of health is unreasonable and capricious, is an unreasonable exercise of the police power and violates constitutional prohibition. It has no real and substantial relation to the public health or any other subject important to public welfare. The requirement of the standard bears no relation to the sanitary conditions or the adequacy of the equipment of the hospital; no relation to the training, competence, or qualification of the personnel, or to the manner of the operation of the physical plant of the hospital; and no relation to the public health, morals, welfare, or security.

Any standard adopted by the department of health, said the Supreme Court, must meet constitutional requirements, must not be oppressive, arbitrary, or discriminatory, nor disregard substantial property rights. The practice of osteopathy is recognized and authorized by law. It is constituted a lawful occupation in the public interest and as such is entitled to protection against unlawful restrictions and interference. It may not be arbitrarily limited or discriminated against, and its advocates may lawfully erect and operate buildings and facilities for the treatment, according to its tenets, of patients seeking its aid, subject to lawful and reasonable limitations and regulations under the police power. The limitations and regulations imposed must bear relation to the public health or welfare. The practice of the plaintiff as an osteopath is his business, it is a property right, and as such he is entitled to protection against unlawful restrictions and interference. A state or an agency of it may not, under the guise of protecting the public, arbitrarily interfere with private business, prohibit lawful occupations, or impose unreasonable or unnecessary restrictions on them. To grant the plaintiff authority to practice osteopathy and then deny the right to use a recognized and useful facility for the care of his patients, except on condition that he surrender the care of them to a physician and surgeon, is to take away much of the value and importance of the grant made. The record wholly fails to show any reason why the application of the plaintiff should not have been granted and a license issued to him to operate his hospital.

Accordingly, the judgment of the district court was reversed and the cause remanded with directions to render a judgment granting the plaintiff the license to maintain and operate his hospital as requested. *Morgan v. State, 51 N.W. (2d) 382 (Nebraska 1951).*

MEDICAL LITERATURE ABSTRACTS

UNITED STATES

A.M.A. Arch. Dermat. and Syphilol., Chicago

66:299-426 (Sept.) 1952

Dermatology at the Crossroads: Presidential Address. E. A. Oliver. —p. 299.
Local Action of Steroids on Senile Human Skin. J. W. Goldzieher, I. S. Roberts, W. B. Rawls and M. A. Goldzieher.—p. 304.
Review of Psychotherapy of Warts. H. V. Allington.—p. 316.
Inflammatory Nodose Lesions of Lower Leg. H. E. Michelson.—p. 327.
Observations on Pharmacologic Responses of Voerner's Nevus Anemicus. F. Butterworth and J. D. Walters.—p. 333.
Mixed Tumor of Lip. E. P. Cawley and C. E. Wheeler.—p. 340.
Pemphigus Vegetans: Clinopathologic Correlation. W. Director.—p. 343.
Tumor-Like Keratoses: Report of Case. M. T. Fliegelman and A. B. Loveman.—p. 353.
Diethylstilbestrol in Treatment of Senile Sebaceous Adenoma. W. C. Lobitz Jr. and D. P. Cole.—p. 358.
Cicatrizing Tinea Capitis Caused by Trichophyton Rubrum (Trichophyton Purpureum). M. Moore, R. Q. Crotty and C. W. Lane.—p. 363.
*Clam Digger's Dermatitis: Schistosome Dermatitis from Sea Water. L. Orris and F. C. Combes.—p. 367.
Gargoylism with Cutaneous Manifestations. H. N. Cole Jr., R. C. Irving, H. Z. Lund and others.—p. 371.
*Ulcers of Leg in Felty's Syndrome. E. P. Schoch Jr.—p. 384.

Clam Diggers' Dermatitis.—"Arming" for hard clams is done in shallow water. The "armer" stirs up the mud with his hands and scoops in the clams. Most clam diggers wear rubber gloves and three or four pairs of nylon stockings to cover both arms from wrists to shoulders. The young man whose case is reported was a novice at clam digging and wore no protective clothing. Several hours later he experienced intense itching of the arms. The following morning he observed numerous discrete, red, "hive-like" papules on both forearms. These were initially about 2 mm. in diameter but gradually enlarged to about 1 cm., their summits capped by a seropurulent crust. Although new lesions appeared daily, the patient continued to scoop clams. By the fifth day, both upper extremities were red, swollen, painful, and covered by several dozen nodules. He applied an antihistaminic cream and hot saline compresses without relief. Elevation of temperature to 101 F, malaise, and chilliness failed to respond to antihistamine tablets. On the seventh day (three days after the last exposure), he was extremely uncomfortable, chilly, and feverish. Both forearms and hands were red, hot, edematous, painful, and covered by an eruption. The patient was treated with cold compresses, a shake lotion, penicillin given intramuscularly, and antihistamines given orally. Within 24 hours he was much improved, and when he was last seen, seven weeks later, the eruption had disappeared except for some residual pigmentation, slight infiltration, and superficial desquamation. This eruption in clam diggers is identical clinically to that in cases of schistosome dermatitis ("swimmers' itch"). Although reportedly fresh-water parasites, Schistosoma cercariae must also be able to live in salt water.

Ulcers of Leg in Felty's Syndrome.—Two patients in whom leg ulcers concurred with Felty's syndrome (chronic rheumatoid arthritis, splenomegaly, and leukopenia) are described. Schoch says that three cases of this type have previously been reported in the literature. He doubts that Felty's syndrome is actually an entity; rather it seems to be a fortuitous coincidence of arthritis with some form of hypersplenism that causes leukopenia. Arthritis is a chronic inflammatory (infectious) disease that has been shown to be a generalized process. Splenomegaly, leukopenia, anemia, weight loss, liver dysfunction, depression of the bone marrow, vasomotor abnormalities, and fibrosis and atrophy of the skin have been found associated with arthritis. It is conceivable that ulceration of the skin could result from several of these factors, yet in rheumatoid arthritis alone ulcers of the leg rarely, if ever, occur. The formation of leg ulcers in the cases presented here is thought to be due mainly to the persistent leukopenia, because this was the most consistent manifestation throughout the clinical courses. A few so-called L. E. cells were described as occurring in the bone marrow in one case. It has been suggested that some instances of "Felty's syndrome" may be cases of latent lupus erythematosus.

A.M.A. Ind. Hyg. & Occupat. Med., Chicago

6:199-292 (Sept.) 1952

Air Pollution by Hydrogen Sulfide in Poza Rica, Mexico: Evaluation of Incident of Nov. 24, 1950. L. C. McCabe and G. D. Clayton.—p. 199.
Retention, Distribution and Elimination of Inhaled Particulates: With Particular Reference to Evaluation of Radiologic Risk. M. Eisenbud —p. 214.
Rapid Analytical Method for Air-Pollution Surveys: Determination of Total Particulates and Rapid Semiquantitative Spectrographic Method of Analysis of Metallic Constituents in High-Volume Samples. R. G. Keenan and D. H. Byers.—p. 226.
Studies on Toxicity and Skin Effects of Compounds Used in Rubber and Plastics Industries. II. Plasticizers. F. S. Mallette and E. von Haam. —p. 231.
Id.: III. Carcinogenicity of Carbon Black Extracts. E. von Haam and F. S. Mallette.—p. 237.
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Eye Health Evaluation and Maintenance. A. K. Peterson.—p. 248.
Parathion Exposure and Cholinesterase Response of Quebec Apple Growers. K. Kay, L. Monkman, J. P. Windish and others.—p. 252.
Pharmacological Studies of Radiogermanium (GE^{71}). H. C. Dudley and E. J. Wallace.—p. 263.
Rapid Micromethod for Electrometric Determination of Red Cell Cholinesterase Activity in Whole Blood. W. E. MacDonald Jr., C. B. Pollard and A. H. Gropp.—p. 271.

A.M.A. Arch. Neurology and Psychiatry, Chicago

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Brain of Patient A. After Bilateral Frontal Lobectomy: Status of Frontal-Lobe Problem. R. M. Brickner.—p. 293.
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Communicating Hydrocephalus from Diffuse Meningeal Tumor: Report of Two Cases with Increased Intracranial Pressure Treated by Use of Polyethylene Tube. A. W. Adson, H. W. Dodge Jr. and J. W. Kernohan.—p. 329.
Vascular Malformations of Spinal Cord. S. Brion, M. G. Netsky and H. M. Zimmerman.—p. 339.
Study of Syndromes of Denial. T. C. Guthrie and E. M. Grossman. —p. 362.
Desoxycorticosterone Therapy in Certain Psychotic Cases: Interval Report. R. Jens.—p. 372.
Disturbances of Vibratory Sense (Pallesthesia) Associated with Nerve Root Compression Due to Herniated Nucleus Pulposus. B. L. Wise. —p. 377.
*Denial of Illness: Its Occurrence in 100 Consecutive Cases of Hemiplegia. M. Nathanson, P. S. Bergman and G. G. Gordon.—p. 380.
Studies on Proteolytic Enzyme System in Schizophrenia. J. S. L. Jacobs and C. E. Tempereau.—p. 388.
Analysis of Cerebral Control of Reflex Pupillary Dilation in Cat and Monkey. W. C. Wilson.—p. 393.

Denial of Illness.—The denial of illness was studied by Nathanson and associates in 100 consecutive patients with hemiplegia. All patients were asked the same question and given the same commands with regard to the involved part, such as: Is there anything wrong with it? Can you move it? Is it weak, paralyzed, or numb? Twenty-three patients of this group unequivocally and consistently denied that their extremities were weak or paralyzed, and claimed that they could move them. Five patients, although they sometimes gave evidence of awareness

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Titles marked with an asterisk (*) are abstracted.

of their illness, for the most part denied their defects. Thus denial of illness is fairly common, occurring in 28% of these patients with hemiplegia. The authors suggest that the incidence might be higher, since many of their patients could not be tested because of severe aphasia. Other groups of hemiplegic patients might yield a lower or higher incidence of denial of illness, depending on the number of cases of left and right hemiplegia, the number of cases of severe aphasia, the type of hospital (psychiatric or general), and, to a certain degree, the attitude of the investigators. Expressions of denial of illness by the patient are often overlooked by the physician, because they do not appear relevant to the symptoms of which the patient does complain. Many of the patients cited here readily admitted that they were "sick" and described many unrelated symptoms, but stated that nothing was wrong with their extremities, even when confronted with the fact that they were paralyzed. The nature and character of the remarks made by the patients suggest some of the underlying mental processes involved in this phenomenon. Denial of illness was always associated with an "organic mental syndrome" and occurred in a much higher proportion of cases of left hemiplegia. It also occurred, however, with lesions of the "dominant" hemisphere. Associated phenomena were rationalizations, confabulations, duplications, denial of the existence of an extremity, denial of other illnesses, and disorientation.

A.M.A. Arch. Otolaryngology, Chicago

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A.M.A. Archives of Surgery, Chicago

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Gastric and Jejunal Alimentation with Fine Polyethylene Tubes. L. S. Fallis and J. Barron.—p. 373.
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American Journal of Medical Sciences, Philadelphia

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Hydriodide of Diethylaminoethylester Penicillin-G, Neopenil, III: Unusually High Penicillin Concentrations in Cerebrospinal Fluid Following Intramuscular Administration. N. H. Schimmel, W. W. Wilson, W. V. Matteucci and H. F. Flippin.—p. 247.
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Comparative Study of Ascorbic Acid Levels in Gastric Secretion, Blood, Urine and Saliva. II. Saturation Studies. R. Hafkesbring and J. T. Freeman.—p. 324.
Experimental Rheumatic Carditis, Periarteritis Nodosa and Glomerulonephritis. S. D. Kobernick.—p. 329.
Premature Birth as Problem of Human Populations. L. Corsa Jr., T. F. Pugh, T. H. Ingalls and J. E. Gordon.—p. 343.

Vitamin B_{12} in Viral Hepatitis.—Three groups of 100 patients each with acute viral hepatitis were studied. The groups were comparable as regards age, race, duration of illness and degree of icterus. Group 1 received the conventional treatment, consisting of a high-protein, high-carbohydrate, moderate-fat diet, bed rest, multivitamins, and brewer's yeast. Group 2 received the same diet and bed rest without added vitamins or brewer's yeast. Group 3 received the same treatment as group 2, but with the addition of 30 μg of vitamin B_{12} orally for the first five days of hospitalization. The patients who received vitamin B_{12} had a more rapid return to normal appetite and liver size than the patients in the other two groups. The total serum bilirubin values of all of the patients in the vitamin B_{12} group were normal after the 10th week of illness, whereas 18 weeks were required by group 2, and 24 weeks by group 1. The mean duration of illness, calculated from the date of the onset of the first symptom to the date the liver function tests became normal and remained so, was 48.7 days for the patients who received vitamin B_{12}, 54.4 days for those in group 2, and 56.7 for those in group 1. There were five instances of relapse in group 1, four such instances in group 2, and only two among the patients given vitamin B_{12}. Experimental work links vitamin B_{12} to nucleoprotein metabolism and hence to liver repair. Its role as a lipotropic agent is further evidence of its importance in liver diseases. The relationship of vitamin B_{12} to folic acid in this process is considered. Despite the absence of controls given placebo preparations resembling vitamin B_{12} and the objectionable method of not selecting the patients at random, the results obtained warrant further investigation.

Amphetamine Sulfate in Barbiturate Poisoning.—Amphetamine (benzedrine®) sulfate was given to 11 patients between the ages of 20 and 77 with barbiturate poisoning. Doses of up to 100 mg. every half to one hour were administered. The total dose of amphetamine sulfate varied from 40 to 700 mg. There were no deaths, even though two patients were first seen in a state of respiratory arrest and circulatory collapse. Consciousness was restored within 6 to 26 hours in 10 patients. One patient, because of her clinical condition, did not receive any medication for occasional periods of three to four hours and regained consciousness within four days. It is felt, however, that the return to consciousness would have been more prompt if the drug had been given more energetically. Results obtained in the author's

patients confirmed the favorable results reported in 160 cases collected from the literature. No convulsions could be elicited even with very large doses of amphetamine sulfate. Thus amphetamine sulfate because of its safety and its prompt effectiveness if given repeatedly in sufficiently large doses, appears to be the ideal analeptic combined with rational supportive therapy in the treatment of severe barbiturate poisoning.

American Journal of Ophthalmology, Chicago

35:1241-1406 (Sept.) 1952

Ocular Cystinosis. H. G. Guild, F. B. Walsh and R. E. Hoover.—p. 1241.
*Studies on Effect of High Oxygen Administration in Retrolental Fibroplasia. I. Nursery Observations. A. Patz, L. E. Hoeck and E. De La Cruz.—p. 1248.
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Optic Atrophy in Infancy, Childhood, and Adolescence: Survey of 81 Cases. F. C. Cordes.—p. 1272.
Cataract Extraction in One-Eyed Patient: Study of 103 Consecutive Cases. A. Callahan.—p. 1285.
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Experimental and Clinical Observations of Effects of Cortisone in Corneal Lesions. W. M. James, J. L. Power and P. H. Ripple.—p. 1298.
Historic and Ethnologic Factors in Distribution of Trachoma. J. Taborisky.—p. 1305.
Complications of Cataract Surgery. C. D. Townes, C. T. Moran and H. A. Pfingst.—p. 1311.
Importance of Corrected Curves in Spectacle Lenses. P. W. Miles. —p. 1320.
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Sulfonamides in Trachoma. A. E. Diab and C. N. Abu-Jaudeh.—p. 1339.
Use of Furacin in Ophthalmology. J. W. Brennan.—p. 1343.
Electroretinography: Clinical Survey. J. H. Jacobson and J. M. O'Brien. —p. 1346.
Detection of Intraocular Spectacle-Glass Foreign Bodies. J. Zwanger, R. Gilroy and H. L. Jones.—p. 1349.

Oxygen Administration in Retrolental Fibroplasia.—Of 65 infants with birth weights under 3.5 lb. (1,534 gm.), 28 were maintained in high oxygen concentrations (65 to 70%) for four to seven weeks; the remaining 37 infants received lower oxygen concentrations (under 40%). The nursery routine was otherwise identical in the two groups. Retrolental fibroplasia occurred in 17 of the 28 infants receiving high concentrations of oxygen over prolonged periods. Of these 17 infants, 7 progressed to grade 3 of the disease, representing detachment of retina, new vessel formation, retinal hemorrhages, and vitreous opacities, or to grade 4 retrolental fibroplasia, representing the completely arrested disease with residual retrolental membranes. Retrolental fibroplasia occurred in 6 of the 37 infants in the lower oxygen group, but none of them progressed beyond grade 2 changes, i. e. vascular changes, increased retinal edema, retinal hemorrhages, and vitreous clouding and opacities. Diminishing the retinal blood flow, altering the retinal enzyme systems, or exposing the developing retina to relatively higher oxygen tensions are the possible methods by which elevated oxygen tensions might influence the developing premature retina. Examination immediately prior to removal from the incubator revealed dilation and tortuosity of the retinal vessels, vitreous haze, and an index myopia of approximately six diopters in two of the infants reported on. Instead of being gradually weaned from oxygen, as is done routinely, these infants were suddenly removed from constant 70% oxygen to room oxygen (20%). Subsequent examinations demonstrated a spontaneous regression of their mild retrolental fibroplasia to normal despite the anoxic insult that resulted from the sudden withdrawal from a high oxygen environment. It is suggested that prolonged high oxygen, if injurious, results from a direct effect instead of from the relative anoxia that might result from the too rapid withdrawal from oxygen. In view of the bizarre manner in which the disease fluctuates, additional rigidly controlled observations are necessary to establish the concept that high oxygen administration is a factor in the pathogenesis of retrolental fibroplasia. There are now sufficient data to question the advisability of the "routine" use of prolonged high oxygen concentrations in the nursery.

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American Journal of Surgery, New York

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*Rupture of Intervertebral Disc in Industry: Further Observations on End Results. A. P. Aitken.—p. 261.
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Multiple Mesothelial Cysts of Peritoneum. J. S. Krieger, E. R. Fisher and M. R. Richards.—p. 328.
Recurrent Appendicitis in Each Trimester of Pregnancy, With Case Report in Each Trimester. M. B. Jorgensen.—p. 331.
*Transection of Coronary Artery During Course of Mitral Valvular Commissurotomy. L. L. Lane, F. C. Massey and C. P. Bailey.—p. 335.

Rupture of Intervertebral Disk.—Strain of the low back brought on by lifting or twisting is variously described as occurring in the low back muscles or in the various intraspinal ligaments. Others believe that the lesion occurs in the capsules of the articular facets. Rupture of an intravertebral disk is generally assumed if the pain radiates into the lower extremity. Although recognition of ruptured intervertebral disk as a cause of lesions of the low back represents an advance, there is doubt that all lesions characterized by back and leg pain are to be explained on such a basis. A résumé is given of the end results of 200 patients operated upon for rupture of the intervertebral disk between the years 1947 and 1949. There was little if any improvement over a comparable series treated during the years from 1940 to 1947. The diagnosis was erroneous in 17.5% of the cases. Diagnostic criteria including distribution of pain, effect of coughing and sneezing on pain, total protein determination, myelogram and neurologic findings, and the fallibility of any or all symptoms, tests or findings are pointed out. Conservative treatment should be tried first, because it may help to clarify the diagnosis. The author does not condemn the operation for rupture of the intervertebral disk, but he deplores the lack of adequate study, the failure to appreciate psychological effects of injury, the unconcern with which surgery is recommended, and the inadequacy of its performance by some surgeons. If these deficiencies are corrected, there will be a decrease in the volume of surgery with a vast improvement in end results.

Transection of Coronary Artery During Valvular Commissurotomy.—Transection of the circumflex branch of the left coronary artery incident to the performance of mitral valvular commissurotomy occurred twice during the course of 282 mitral valvular commissurotomies. One of the two cases is presented in detail. Toward the end of the operation a peculiar cardiac rhythm developed, which suggested that there was appreciably diminished cardiac output. The operation was terminated, the pleura was flushed and drained, and the thoracotomy incision was closed in layers. The patient became increasingly restless and writhed as though in extreme pain despite sedation. Medium crepitant rales were audible over the left chest, and there was pallor. About 40 minutes later the patient suddenly became violently agitated, hyperkinetic, hyperpneic, and cast his head backward in opisthotonic extension. A dramatic change from extreme pallor to intense cyanosis preceded only momentarily the abrupt cessation of respiration and death. Surgical division or partial division of the circumflex branch of the left coronary artery from within the cardiac chamber is possible if the valvular division is carried not only to the myocardial wall but actually into it. The location of the artery deep within the pad of fat occupying the atrioventricular groove renders this risk inherent in commissurotomy either by the instrumental or the digital pressure technique. In a second case the failure to keep the guillotine closed during the intracardiac manipulations other than the definitive valvulotomy may have been primarily responsible for the accident. The puzzlingly late appearance of the symptoms of transection (45 minutes after the conclusion of the operative procedure) resembled the clinical picture produced by spontaneous rupture of the left ventricle following acute myocardial infarction. Other conditions that are brought to mind and must be considered in the differential diagnosis are acute cardiac dilatation, mitral insufficiency, acute myocardial infarction, pulmonary embolism, ventricular fibrillation, and complete heart block.

Am. J. Tropical Medicine & Hygiene, Baltimore

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Densities of Anopheles, Sporozoite Rates in Anopheles, and Incidence of Malaria in Area of South Carolina. F. O. Atchly.—p. 743.

Epidemic of Acute Anterior Poliomyelitis in Panama in 1950-1951. A. Rodaniche and E. C. de Rodaniche.—p. 784.

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Three New Potential Intermediate Hosts of Human Onchocerciasis in Guatemala. C. L. Gibson and H. T. Dalmat.—p. 848.

Failure of Aureomycin in Treatment of Schistosomiasis. J. A. Hightower and P. M. Bauman.—p. 852.

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Adenoid Cystic Carcinoma (Cylindroma) of Bronchial Tree. J. D. Reid. —p. 685.

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Congenital Neurofibromatous Macroglossia Associated in Some Cases with von Recklinghausen's Disease: Case Report and Review of Literature. W. W. Ayres, A. J. Delaney and M. H. Backer.—p. 721.

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Extensive Carcinoma in Situ in Bronchial Mucosa Associated with Two Invasive Bronchogenic Carcinomas: Report of Case. M. J. Williams. —p. 740.

Cancer of Female Urethra. R. M. Ruch, J. B. Frerichs and A. N. Arneson.—p. 748.

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Evaluation of Surgical Treatment of Carcinoma of Head of Pancreas. E. S. Brintnall.—p. 908.

Multiple Microscopic Primary Bronchiolar Carcinomas: Report of Case with Discussion of Histogenesis. J. B. Horrell and J. S. Howe.—p. 911.

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Liposarcoma Arising Within Subcutaneous Lipoma. S. S. Sternberg. —p. 975.

Radical Mastectomy in Continuity with En Bloc Resection of Internal Mammary Lymph-Node Chain: New Procedure for Primary Operable Cancer of Breast. J. A. Urban and H. W. Baker.—p. 992.

*Effect of Bilateral Adrenalectomy Upon Neoplastic Disease in Man. C. D. West, V. P. Hollander, W. F. Whitmore, Jr. and others. —p. 1009.

*Physiological Effects of Bilateral Adrenalectomy in Man. V. P. Hollander, C. D. West, W. F. Whitmore, Jr. and others.—p. 1019.

Clinical Studies of Viruses as Antineoplastic Agents, with Particular Reference to Egypt 101 Virus. C. M. Southam and A. E. Moore. —p. 1025.

Value of Mass Chest Roentgen-Ray Survey Methods in Control of Lung Cancer. L. W. Guiss.—p. 1035.

Effect of Bilateral Adrenalectomy on Neoplasms. — Bilateral adrenalectomy was performed on 22 patients with advanced cancer since February, 1951. Of these 22 patients, 10 had carcinoma of the prostate, 6 carcinoma of the breast, 2 carcinoma of the cervix, 1 carcinoma of the colon, 1 malignant melanoma, 1 acute myelogenous leukemia, and 1 leiomyosarcoma of the uterus. The rationale for bilateral adrenalectomy in patients with neoplastic disease is based on both clinical and experimental evidence that the adrenal gland is involved in the growth of neoplastic tissue. Of the 22 patients, 18 were followed long enough for evaluation. Bilateral adrenalectomy was not curative in any of the authors' patients. Of the 10 patients with prostatic cancer, 3 died within 30 days postoperatively, leaving 7 effective cases for evaluation. All seven patients had temporary striking subjective improvement, i. e. relief of pain and improvement in general condition. Only two patients showed objective evidence of tumor inhibition lasting 90 to 133 days. One of the six patients with breast cancer died too soon for therapeutic evaluation. The remaining five showed subjective improvement lasting from 14 to 120 days, and two of these patients showed objective improvement for approximately 120 days. None of the six patients with miscellaneous neoplastic diseases was benefited

by adrenalectomy. In this study no major therapeutic benefits were observed. In most patients there has been progression of the neoplastic disease by objective criteria in the face of subjective improvement. However, definite evidence of temporary inhibition of tumor growth was shown by four patients, so that further investigation of the effects of adrenalectomy in patients with breast and prostate cancer is indicated.

Physiological Effects of Bilateral Adrenalectomy in Man.—In the 22 patients subjected to bilateral adrenalectomy for neoplastic disease, cortisone alone was used as replacement therapy. The acute stress of surgery demanded large quantities of cortisone. Two regimens for replacement therapy were developed. The intravenous regimen is illustrated by a patient who received 300 mg. free cortisone in 5% dextrose in water by continuous infusion on the day of operation, 200 mg. the following day, and 100 mg. on the second postoperative day. On this day oral administration of cortisone acetate was begun in a dose of 50 mg. every six hours. This dose was gradually decreased until the patient was maintained on 37.5 mg. daily. The intramuscular regimen for cortisone replacement is illustrated by a patient who the day before surgery received a total of 300 mg. of cortisone acetate intramuscularly in divided doses. One hour before surgery he received 100 mg. of cortisone acetate orally. On return from surgery 50 mg. of cortisone acetate were given intramuscularly every three hours, and the following day 50 mg. every four hours. On the second postoperative day, maintenance was achieved with oral cortisone acetate, the dose of which was gradually lowered until he received 50 mg. daily in two equal doses. All of the 22 patients were maintained after operation with cortisone acetate orally as the only replacement therapy. The dosage varied from 37.5 mg. to 75 mg. daily in two to four divided doses, the maintenance dosage of cortisone being adjusted to the patient's needs. Physiological studies in these patients suggested that cortisone may represent complete replacement for the normal adrenal cortex. Withdrawal of cortisone therapy in six patients resulted in prompt development of the symptoms and signs of adrenal insufficiency. Physiological changes were characterized by prompt antidiuresis on cortisone withdrawal and prompt water diuresis on resumption of cortisone therapy. These observations indicate that water intoxication is an important feature of the physiological effects of adrenal insufficiency in man. The therapeutic connotations in the recognition of water retention in adrenal insufficiency are discussed.

Connecticut State Medical Journal, Hartford

16:663-722 (Sept.) 1952

Diarrhea in Infancy. S. S. Stevenson.—p. 671.
Early Recognition of Endometriosis and Hormonal Treatment with Testosterone. J. M. Freiheit.—p. 674.
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Effect of Premedication of Cortisone on Healing of Wounds in Infant. A. Rubin and M. D. Lischner.—p. 682.
Standing Orders—Responsibility of Industrial Physician. J. Lieben. —p. 683.
Doctor's Own Mental Health. E. S. Rademacher.—p. 685.

Diabetes, New York

1:257-340 (July-Aug.) 1952

Insulin; Banting Memorial Lecture 1952. C. H. Best.—p. 257.
*Inheritance of Diabetes Mellitus: Analysis of Family Histories of 1,631 Diabetics. M. W. Thompson and E. M. Watson.—p. 268.
Effects of Acidosis on Insulin Action and on Carbohydrate and Mineral Metabolism. G. M. Guest, B. Mackler and H. C. Knowles, Jr.—p. 276.
*Survey of Tuberculosis Among Diabetics. E. S. Dillon, K. R. Boucot, D. A. Cooper and others.—p. 283.
Present Status of New Insulin Modifications. F. B. Peck, W. R. Kirtley and F. C. Ottati.—p. 290.
Amputation of Lower Extremity in Diabetes Mellitus: Follow-Up Study of 294 Cases. S. Silbert.—p. 297.

Inheritance of Diabetes Mellitus.—Familial data obtained from 951 female and 680 male diabetics observed at the Victoria Hospital, London, Ontario were credible for 4,631 siblings. Of these 415 (8.96%) had diabetes mellitus. Of the 3,836 siblings with neither parent diabetic, 295 (7.6%) had diabetes, and of the 771 siblings with one diabetic parent, 118 (15.3%) had diabetes. The observation that the proportion of affected siblings when one parent was diabetic was approximately twice as great as when neither parent was so affected is suggestive of inheritance by a single autosomal recessive gene. Diabetes mellitus appeared with approximately equal frequency in the siblings regardless of the onset age of the diabetic propositi. Of the 3,262 parents of the 1,631 diabetic propositi, diabetes mellitus was known to be present in 231 (7.08%). Parenteral consanguinity occurred in nine instances (0.55%). There was no apparent tendency for diabetes mellitus to affect chiefly males in some lineages and chiefly females in others. The observed slight excess of like-sexed sibling pairs and parent-offspring pairs is explicable on the basis of the sex ratio of diabetes mellitus in general.

Tuberculosis Among Diabetics.—Of 3,106 patients with diabetes mellitus, 261 (8.4%) had tuberculosis compared with 4.3% in a group of apparently healthy industrial workers adjusted to correspond to the distribution by age, sex, and race of the diabetic group. Of the 261 diabetics with tuberculosis, 80 (2.6%) had active tuberculosis, which was three times as prevalent in those less than 40 years of age as in those aged 40 and over. The prevalence of active tuberculosis increased pronouncedly with the severity of the diabetes mellitus. In the younger age group the prevalence of active tuberculosis was much greater in those who had had diabetes mellitus 10 years or more. The prevalence of tuberculosis was much greater in underweight patients than in those who were overweight. Tuberculosis was much more likely to be active in diabetics than in nondiabetics.

Diseases of Chest, Chicago

22:245-368 (Sept.) 1952

*Hypothermia as Means of Performing Intracardiac Surgery Under Direct Vision. B. A. Cookson, W. B. Neptune and C. P. Bailey.—p. 245.
Cor Pulmonale (Pulmono-Cardiac Syndrome): Case Report. C. S. Lewis, M. C. Daines, A. J. Samuels and H. H. Hecht.—p. 261.
Coronary Circulation in Patients with Severe Emphysema, Cor Pulmonale, Cyanotic Congenital Heart Disease, and Severe Anemia. H. A. Zimmerman.—p. 269.
Pectus Excavatum. F. M. Woods, R. H. Overholt and H. E. Bolton. —p. 274.
Clubbing of Digits as Primary Disease. M. C. McCord and H. L. Hyman. —p. 283.
Influence of Cortisone on Tuberculin Shock in Guinea Pig. M. M. Cummings and P. C. Hudgins.—p. 289.
*Primary Tuberculosis Acquired in Adulthood. J. A. Meyers.—p. 293.
Practical Significance of Tuberculous Infection with Streptomycin-Resistant Organisms. L. S. Arany.—p. 313.
Recovery of Pulmonary Function After Crushing Injuries of Chest. N. K. Jensen.—p. 319.
Bronchogenic Carcinoma and Chromates. S. Imprescia.—p. 347.
Fibrinous Pericarditis Secondary to Esophageal Ulceration. G. E. Muehsam.—p. 356.

Hypothermia in Intracardiac Surgery.—For the performance of intracardiac surgery under direct vision it is necessary to interrupt temporarily the flow of blood through the heart. Because of the demands of the body for oxygen under ordinary circumstances, however, the circulation can be interrupted in this way for only a few minutes. The authors felt that this period might be prolonged, and more extensive intracardiac surgery made possible, if they could temporarily reduce the oxygen demands of the body by means of induced hypothermia during operation. In animals it is possible to reduce rectal temperatures safely to 26 C (79 F), and this lowers the oxygen requirements to 18% of its normal value. Using hypothermia of this type the authors occluded the vena cava of 32 dogs for 12 to 30 minutes and performed relatively bloodless cardiotomy of the right auricle and ventricle. Following the relief of the caval occlusion, the occurrence of ventricular fibrillation was prevented by injecting piperoxan (benodaine®) hydrochloride, a short acting adrenolytic drug, into the ventricular chamber. With caval occlusion for 12 minutes 80% of the animals survived, and with caval occlusion for 30 minutes 40% survived. This much time would obviously be sufficient for definitive surgery upon the valves and septums. The authors believe that their method will be useful in the surgical management of various disorders of the circulatory system in man, particularly of defects of the auricular and ventricular septums.

Primary Tuberculosis in Adulthood.—From 1920 to the present, the author has observed at intervals the tuberculin reactions of more than 19,000 children and many thousand adults. Several hundred were observed who first became reactors to tuberculin

in adulthood. Many of them, particularly students of nursing and medicine, were periodically tested with tuberculin every 6 to 12 months. Therefore the time when they became infected was determined with reasonable accuracy. In the United States primary tuberculosis develops oftener in adults than in children, since the annual infection attack rate is essentially the same (0.3% in cities and less in rural areas) in the two groups and since the period of adulthood is more than three times longer than that of childhood. Primary lesions that develop in adults are usually benign and present the same allergic manifestations in approximately the same proportion as in children. Atelectasis is less frequently seen in adults primarily infected, probably because of the larger size and more rigid walls of the bronchi. Observations revealed that the theory that primary tuberculosis in adulthood is more serious than that acquired in childhood is untenable. Since roentgen ray shadows are not pathognomonic, there is no possibility of differentiating between primary and reinfection type of lesions by the shadows they cast. Lesions that appear about the time tissues become sensitive to tuberculin are almost always primary, while those that appear months or years later are due to reinfection from endogenous or exogenous sources. The time when tissues become sensitive to tuberculoprotein is the determining factor in differential diagnosis. The management of primary tuberculosis is the same in adults and children. All adults with primary tuberculosis, whether it is acquired in childhood or adulthood, should be examined periodically for possible acute or chronic reinfection and advised to report promptly if symptoms appear suggestive of meningitis, pneumonia, miliary disease and pleurisy. The only dependable method of preventing adults from acquiring primary tuberculosis is to bar tubercle bacilli from their bodies. Introduction of organisms of reduced virulence produces primary lesions. Proper management of cases of tuberculosis and strict contagious disease technique have proved to be efficacious.

Gastroenterology, Baltimore

21:483-620 (Aug.) 1952

*Congenital Dysplasia of Interlobular Bile Ducts with Extensive Skin Xanthomata: Congenital Acholangic Biliary Cirrhosis. H. E. MacMahon and S. J. Thannhauser.—p. 488.
Implications of Failure of Gastroscope to Pass Cardiac Orifice of Stomach. S. Selesnick and B. V. White.—p. 507.
*Repeated Blood Volume Determinations in Bleeding Peptic Ulcer. S. Kruger, L. Baker and W. D. Mosiman.—p. 516.
Amebiasis: Some Features of Disease Revealed by Study of Autopsy Material From 9 Cases. R. A. Radke.—p. 525.
Experience with New Cholecystographic Medium (Telepaque). F. M. Spencer.—p. 535.
Guaiac Test—Correlation with Clinical Findings. R. N. Barnett.—p. 540.
New Instrument for Gastric Biopsies Under Visual Control. J. Tomenius. —p. 544.
Gastric Acid Response to Massive Doses of Insulin: I. Prolonged Observations on One Individual. E. M. Levy, A. P. Dell Cort and V. W. Logan. —p. 547.
Shay Rat as Assay Animal for Anti-Ulcer Factors: III. Paper Chromatography and Other Chemical Studies of Shay Rat Anti-Ulcer Factors. H. L. Segal, L. L. Miller, R. P. Plosscowe and L. M. Haroutunian. —p. 551.
Id.: IV. Effect of Adrenalectomy and Nephrectomy. L. M. Haroutunian and H. L. Segal.—p. 556.
Comparative Study of Effect of Oral and Subcutaneous Banthine on Gastric Secretion from New Innervated Gastric Pouch. R. A. Forse, L. J. Notkin and D. R. Webster.—p. 561.
Effect of Lysozyme on Canine Gastrointestinal Mucosa; Further Study. E. C. Meadows and J. Levison.—p. 569.
Effect of Bentyl Hydrochloride on Choledocho-Duodenal Region in Dogs. E. Esses, D. F. Magee and A. C. Ivy.—p. 574.

Congenital Acholangic Biliary Cirrhosis.—MacMahon and Thannhauser observed a very unusual type of liver disease in a 10-year-old boy. Jaundice had been observed a few days after birth and had persisted, although it intermittently decreased and increased. For years he had complained of intense itching. Gradually several yellow skin lesions appeared, and, at the age of 8 years, these lesions spread over the entire body. Similar but more whitish lesions appeared in the gingiva and the oral mucous membranes. The patient underwent herniorrhaphy two years previously. He had had many nosebleeds in the last years. His appetite was good. Stools were very light in color and of mushy consistency. The urine was always dark brown. The liver and spleen were enlarged. Two diagnoses had been considered, before an abdominal exploration was decided on: (1) incomplete atresia of the common bile duct, (2) xanthomatous biliary cirrhosis (pericholangiolitic biliary cirrhosis). The first diagnosis was ruled out by laparotomy and the second by liver biopsy, which revealed a congenital dysplasia of the interlobular bile duct system. This case shows that such a lesion can produce a clinical syndrome similar to that produced by an inflammatory obliteration of these bile ducts (pericholangiolitic biliary cirrhosis or xanthomatous biliary cirrhosis). It suggests that the amount of cholesterol and phospholipids present in the serum depends on the function of this part of the liver. It throws light on the embryogenesis of liver cells and bile ducts. It offers a basis for explaining certain primary tumors of the liver displaying characteristics of both liver cells and bile ducts. It points to the junction ducts of perilobular ducts as an important element in the regeneration of damaged livers. It suggests that in cases of the well-known dysplasias of the extrahepatic ducts, a thorough histological study should be made of the intrahepatic biliary system to ascertain whether or not the intrahepatic bile ducts are also altered in this type of congenital anomaly. Because this congenital malformation led to a mild type of biliary cirrhosis the term "congenital acholangic biliary cirrhosis" is suggested for this disease of the liver. This type of cirrhosis can be distinguished only by biopsy from acquired pericholangiolitic biliary cirrhosis. Both of these types of biliary cirrhosis should be distinguished from the simple cholestatic and cholangitic types that are associated with bile stasis and bile duct infection, respectively.

Blood Volume Determinations in Bleeding Peptic Ulcer.—There is no truly accurate index to guide the clinician in blood replacement. Estimates are usually based on the erythrocyte count, hemoglobin concentration, and hematocrit level. Although these criteria are usually adequate, determination of blood volume may add considerable information. However, a single determination obviously does not reveal dynamic compensatory changes, fails to measure volume changes relative to transfusions, and is of no value in determining whether bleeding has ceased or is continuing. The appraisal of this single point often determines whether emergency surgery or conservative therapy will be employed. A total of 61 separate tests were made on 23 patients hospitalized because of bleeding peptic ulcers. Plasma volumes were determined according to the method of Crispell, Porter and Nieset, using human serum albumin tagged with radioiodine (I^{131}). It was found that blood volume determination with radioactive iodinated human serum albumin is a simple, rapid, and safe technique. The severity of the hemorrhage can be objectively measured best by blood volume and total packed red cell volume determinations. Repeated blood volume and total packed red cell volume determinations accurately determine not only the continuation or cessation of active gastrointestinal bleeding but also the quantitative aspects of posthemorrhagic hemodilution and the response to transfusions.

Indiana State Medical Assn. Journal, Indianapolis

45:865-956 (Sept.) 1952

Treatment of Congestive Heart Failure. N. O. Fowler Jr.—p. 881.
*"Adult" Testicular Teratoma in Child: Case Report. B. F. Grotts.—p. 888.
*Carcinoma of Breast: Pathologic Changes Correlated with Diagnosis, Treatment and Prognosis. L. V. Ackerman.—p. 891.
Uteroplacental Apoplexy: Case Report. H. W. Eggers and C. V. Santiago. —p. 900.

Adult Testicular Teratoma in a Child.—The unusual occurrence of adult teratoma of the testis is reported in a 2-year-old boy. An enlarged right testis was noted at birth or shortly thereafter. It seemed to enlarge slowly over the years, but was never painful and remained asymptomatic. There was no weight loss. The right testis and epididymis seemed to be involved in a firm, somewhat nodular, mass about three times normal size. It was felt that his was probably a tumor, but the possibility of a thick-walled hydrocele or hematocele had to be considered. A right orchiectomy was performed with the patient under ether anesthesia. The postoperative course was uneventful, except for an episode of tonsillitis, and the patient was discharged on the 10th postoperative day. Ten weeks after the operation follow-up examination revealed a healed scar with no apparent changes in the opposite testis and still no palpable masses, nodes or viscera. Grossly the removed testicle measured 4.3 cm., with a 7.5 cm. long spermatic cord. When the mass was cut, greasy, gray

material and hairs were noted. The tumor was multicystic and contained spaces up to 3.8 cm. in diameter. Areas of bone formation were present. Microscopic examination revealed sections of infantile testicle compressed by a tumor consisting of organoid structures derived from all three germ layers. These structures included central nervous system tissue with ependymal cells, bronchial tissue, and intestinal tissue. The tumor appeared histologically benign despite a few clusters of glandular epithelial cells, which appeared to be embryonic. A painless persistent swelling in the scrotum in children should be considered a malignant growth until proven otherwise and not merely a simple hydrocele. Testicular enlargement makes exploration or orchiectomy mandatory.

Carcinoma of the Breast.—Ackermann recommends that any patient with a small nodule in the breast should be subjected to surgical intervention in an operating room with facilities for a frozen section, and preferably that the surgeon who operates should be qualified to do a radical mastectomy if the local process demonstrates carcinoma. As a result of study of 587 radical mastectomy specimens, the author states that careful dissection of the axilla with the average number of 25 lymph nodes will demonstrate with a high percentage of accuracy whether the axillary lymph nodes are or are not involved by tumor. There is direct correlation between the size of the tumor and axillary lymph node involvement. The larger the tumor the higher the percentage of axillary lymph nodes involved. It must be emphasized that lymph nodes as small as 2 mm. may be involved. There is little correlation between the grade of the tumor and the presence of metastases. The number of lymph nodes involved is correlated with prognosis: the higher the number the worse the prognosis. Much axillary involvement with involvement of other node groups gives a poor prognosis. The presence of nerve sheath invasion, muscle invasion, or vein invasion in conjunction with lymph node involvement makes the prognosis almost hopeless. Patients with carcinoma arising in an inner quadrant with negative axillary lymph nodes will apparently have distant disease in at least half of the cases, for in the author's experience the survival rate of these patients is 20% less than the over-all survival of all patients without lymph node involvement. In these cases the tumor may spread to the anterior mediastinal lymph nodes, while spread to the supraclavicular lymph nodes is unlikely. A plan of therapy for operable carcinoma of the breast is proposed on the basis of the follow-up of the cases reported and the known channels of spread.

Journal of Allergy, St. Louis

23:387-482 (Sept.) 1952. **Partial Index**

Suggested Quantitative Evaluation of Degree of Sensitivity of Patients with Ragweed Pollinosis. S. M. Feinberg, R. A. Stier and W. C. Grater.—p. 387.

Cortisone in Treatment of Patients with Ragweed Pollinosis Determination of Changes in Sensitivity of Mucosa Produced by Pre- and Co-Seasonal Cortisone Administration. R. A. Stier, S. M. Feinberg, S. Malkiel and M. D. Werle.—p. 395.

Increasing Castor Bean Allergy in Southern California due to Fertilizer. W. S. Small.—p. 406.

Study to Determine the Ability of Cortisone to Sensitize the Skin. M. Grolnick.—p. 416.

Is Skin Testing in Allergic Patients Worth the Effort? V. E. Friedewald. —p. 420.

Is Migraine an Allergic Disease? M. Schwartz.—p. 426.

Migraine is an Allergic Disease. A. H. Unger and L. Unger.—p. 429.

Quantitative Studies in Skin Testing. V. Whealing Reactions of Histamine and Ragweed Pollen Extract. H. H. Swain and E. L. Becker.—p. 441.

Migraine is an Allergic Disease.—Of 11 men and 44 women with classical migraine who were followed for a minimum of three months, 44 (80%) were either completely or almost completely relieved of attacks by detection and elimination of the causative foods. Allergy to food is the prime precipitating cause of attacks. Feeding tests and food diaries are of equal importance in determining the food to which the patient is allergic. The patient should write down everything he ingests for 24 hours before each migraine attack. If certain foods or groups of foods are mentioned repeatedly, these are then eliminated and later tried again to see if symptoms follow. Elimination diets used alone were helpful in 11 of the authors' patients. Feeding tests are used to determine allergy to major foods. Cooperation of the patients is required for three months or longer. A minimum period of two weeks between feeding tests is indispensable to allow an adequate number of tests, if necessary. Statistics are presented to show the relative frequency of various foods known to have caused migraine in the authors' patients. Chocolate was the most important cause, followed by milk, wheat and pork. Diagnosis, differential diagnosis, mechanism, and treatment of attacks of migraine are discussed. It is concluded that migraine is basically an allergic disease, although psychic stimuli may provoke individual attacks in allergic persons.

Journal of Clinical Investigation, New York

31:807-858 (Sept.) 1952

Effect of Breathing 100% Oxygen on Pulmonary Arterial Pressure in Patients with Pulmonary Tuberculosis and Mitral Stenosis. S. H. Dressler, N. B. Slonim, O. J. Balchum and others.—p. 807.

Plasma Cholinesterase Activity in Liver Disease: Its Value as Diagnostic Test of Liver Function Compared with Flocculation Tests and Plasma Protein Determinations. A. Wilson, R. J. Calvert and H. Geoghegan. —p. 815.

Cerebral Circulation and Metabolism in Sickle Cell and Other Chronic Anemias, with Observations on Effects of Oxygen Inhalation. A. Heyman, J. L. Patterson, Jr. and T. W. Duke.—p. 824.

Effect of ACTH on Water Distribution in Man as Measured by Antipyrine, T 1824 and Bromide. M. Ziff, J. Simson and J. J. Bunim. —p. 829.

Alveolar-Arterial Oxygen Pressure Gradient in Mitral Stenosis. S. G. Blount, Jr., M. C. McCord and L. L. Anderson.—p. 840.

Blood Levels of 17-Hydroxycorticosteroids Following Administration of Adrenal Steroids and Their Relation to Levels of Circulating Leukocytes. D. H. Nelson, A. A. Sandberg, J. G. Palmer and F. H. Tyler. —p. 843.

Interrelations of Magnesium, Potassium, Phosphorus, and Creatine in Skeletal Muscle of Man. D. Baldwin, P. K. Robinson, K. L. Zierler and J. L. Lilienthal, Jr.—p. 850.

Journal of Experimental Medicine, New York

96:187-280 (Sept.) 1952

Induction of Arterial Hypertension in Normal and Adrenalectomized Rats Given Cortisone Acetate. A. I. Knowlton, E. N. Loeb, H. C. Stoerk and others.—p. 187.

Growth Requirements of Dysgonic and Eugonic Strains of Mycobacterium Tuberculosis Var. Bovis. W. B. Schaefer.—p. 207.

Relative Effects of Protein, Choline, and Methionine in Treatment of Experimental Dietary Cirrhosis in Rat. I. C. Plough, A. J. Patek Jr. and M. Bevans.—p. 221.

Studies on Psittacosis-Lymphogranuloma Group II. Non-Infectious Phase in Virus Development Following Adsorption to Host Tissue. A. J. Girardi, E. G. Allen and M. M. Sigel.—p. 233.

Plasma Protein Labeled with Lysine-ε-C^{14}. Its Oral Feeding and Related Protein Metabolism in the Dog. C. L. Yuile, A. E. O'Dea, F. V. Lucas and G. H. Whipple.—p. 247.

Survival of Poliomyelitis and Coxsackie Viruses Following Their Ingestion by Flies. J. L. Melnick and L. R. Penner.—p. 255.

Methods for Following Fate of Infectious Agents Fed to Single Flies. L. R. Penner and J. L. Melnick.—p. 273.

Journal Lab. and Clinical Medicine, St. Louis

40:161-320 (Aug.) 1952. **Partial Index**

Statistical Study of Absolute Eosinophil Cell Counts in Healthy Young Adults Using Logarithmic Analysis. R. C. Muehrcke, E. L. Eckert and R. M. Kark.—p. 161.

Epinephrine Eosinopenia in Surgically Induced Addison's Disease. R. C. Muehrcke, T. W. Staple and R. M. Kark.—p. 169.

Adverse Effect of Cortisone on Marrow Regeneration Following Irradiation. J. B. Thiersch, L. Conroy, A. R. Stevens Jr. and C. A. Finch. —p. 174.

Frequency of Laboratory Infections with Histoplasma Capsulatum: Their Clinical and X-Ray Characteristics. M. L. Furcolow, W. G. Guntheroth and M. J. Willis.—p. 182.

Blood Plasma Pepsinogen. II. Activity of Plasma from "Normal" Subjects, Patients with Duodenal Ulcer, and Patients with Pernicious Anemia. A. Mirsky, P. Futterman and S. Kaplan.—p. 188.

Speciation Within Genus Brucella. I. Dye Sensitivity of Smooth Brucellae. M. J. Pickett, E. L. Nelson, R. E. Hoyt and B. E. Eisenstein.—p. 200.

Modified Globin: III. Determination of Modified Human Globin in Blood Serum and in Urine. A. B. Sample, M. M. Strumia and V. Satta.—p. 206.

Id.: IV. Some of Physiological Properties of Modified Human Globin. M. M. Strumia, J. J. McGraw Jr. and A. B. Sample.—p. 211.

Bronchospirometry: III. Complications, Contraindications, Technique, and Interpretation. E. A. Gaensler and T. R. Watson Jr.—p. 223.

Effect of Particle Size on Blood Clearance and Tissue Distribution of Radioactive Gold Colloids. D. B. Zilversmit, G. A. Boyd and M. Brucer. —p. 255.

Mental Symptoms from Myxedema. R. Miller.—p. 267.

Histochemical Characterization of Articular Cartilages of Poliomyelitis Patients. L. Eichelberger, J. S. Miles and M. Roma.—p. 284.

Journal-Lancet, Minneapolis

72:399-460 (Sept.) 1952

Collagen Diseases. G. D. Icenogel.—p. 399.
Biological Effects of Radiation and Factor Which Influence Recovery. W. E. Cornatzer.—p. 403.

Journal Nat. Cancer Inst., Washington, D. C.

13:1-282 (Aug.) 1952. **Partial Index**

Studies on Blood Supply of Tumors in Man. V. Skin Temperatures of Superficial Neoplastic Lesions. H. R. Bierman, R. S. Gilfillan, K. H. Kelly and others.—p. 1.
Modification of Acute Irradiation Injury in Mice and Guinea Pigs by Injection of Bone Marrow: Histopathologic Study. C. C. Congdon, D. Uphoff and E. Lorenz.—p. 73.
Influence of Mammary Tumor Agent on Longevity of Hosts Bearing a Transplanted Tumor. M. K. Barrett, M. K. Deringer and T. B. Dunn.—p. 109.
Effects of Ultrafiltrates and Residues of Horse Serum and Chick-Embryo Extract on Proliferation of Cells in Vitro. K. K. Sanford, H. K. Waltz, J. E. Shannon Jr. and others.—p. 121.
Tumor-Damaging Capacity of Plant Materials. I. Plants Used as Cathartics. M. Belkin and D. B. Fitzgerald.—p. 139.
Agent from E. Coli Causing Hemorrhage and Regression of Experimental Mouse Tumor. I. Isolation and Properties. M. Ikawa, J. B. Koepfli, S. G. Mudd and C. Niemann.—p. 157.
Quantitative Dose-Response Study of Lymphoid-Tumor Development in Irradiated C57 Black Mice. H. S. Kaplan and M. B. Brown.—p. 185.

Journal of Thoracic Surgery, St. Louis

24:213-324 (Sept.) 1952

Localized Fibrous Mesothelioma of Pleura. O. T. Clagett, J. R. McDonald and H. W. Schmidt.—p. 213.
Resection of Trachea for Carcinoma: Report of Two Cases. B. H. Cotton and J. R. F. Penido.—p. 231.
Surgical Treatment of Carcinoma of the Hypopharynx, Larynx, and Upper Esophagus. O. F. Grimes and H. B. Stephens.—p. 246.
Carcinoma of the Esophagus: Consideration of Curative and Palliative Procedures. M. M. Ravitch, T. Bahnson and T. N. P. Johns.—p. 256.
Bronchiogenic Carcinoma, Product of Multiple Sites of Origin. E. J. McGrath, E. A. Gall and D. P. Kessler.—p. 271.
Use of SK-SD (Varidase) in Management of Early Postoperative Partial Pulmonary Resections. C. T. Read.—p. 284.
Rehabilitation in Thoracic Surgery. A. Haas, H. A. Rusk and W. N. Goodman.—p. 304.

Journal of Urology, Baltimore

68:547-666 (Sept.) 1952. **Partial Index**

*Cushing's Syndrome Due to Adrenal Cortical Adenoma. Surgical Cure. G. D. Oppenheimer, J. L. Gabrilove, M. Volterra and H. A. Lear.—p. 547.
Distribution of Renal Ischemia Produced by Epinephrine and Nor-Epinephrine as Demonstrated by Fluorescent Dye Vasoflavine. J. B. Moses.—p. 558.
Nephrectomy for Tuberculosis. N. Chaset.—p. 568.
"Atraumatic" Nephrostomy. A. W. Boone.—p. 574.
Primary Megalo-Ureter. M. Campbell.—p. 584.
Carcinoma of Ureter. A. A. Creecy.—p. 591.
Spontaneous Rupture of Urinary Bladder in Male. M. M. Nemser and H. A. Weinberger.—p. 603.
Traumatic Vesicovaginal and Rectovaginal Fistulas. S. S. Baird and A. D. Green.—p. 608.
Diverticulum of Female Urethra; An Improved Technique of Surgical Excision. T. D. Moore.—p. 611.
Protrusion of Female Urethra. O. de Barros Serra Dória.—p. 617.
*Accidental Transection of All Corpora of Penis: Repair with Good Results. K. A. Price.—p. 620.
*Peyronie's Disease Associated with Dupuytren's Contracture. J. I. Waller and W. C. Dreese.—p. 623.
Carcinoma of Prostate in Young Adults. J. C. Kimbrough and E. L. Lewis.—p. 626.
Cysts of Tunica Albuginea Testis. J. A. Arcadi.—p. 631.
Banthine in Urologic Disorders. L. A. Riskind and H. A. Zide.—p. 636.
Human Serum Albumin for Anuria. F. Cole.—p. 638.
Prostatic and Periprostatic Phlebography. B. S. Abeshouse and M. E. Ruben.—p. 640.
Pelvioprostatic Venography: Preliminary Report. R. J. Fitzpatrick and L. M. Orr.—p. 647.

Surgery for Adrenal Cortical Tumor in Cushing's Syndrome.—Surgical cure of a 26-year-old woman with Cushing's syndrome due to an adrenal cortical adenoma is reported. The patient had had amenorrhea for two years, hirsutism, puffiness of the face, a weight gain of 20 lb. (9.1 kg.) and purple striae over the lateral aspects of her breasts, abdomen and thighs. The basal metabolic rate was —34%. A pronounced kyphoscoliosis and generalized osteoporosis were present. A diagnosis of diffuse bilateral adrenal cortical hyperplasia was made in the absence of an adrenal tumor demonstrable by x-ray. Despite androgenic therapy the osteoporosis increased. Left lumbar adrenal exploration was done arbitrarily and revealed atrophy of the left adrenal gland reflecting the probable presence of a functional contralateral cortical tumor. The atrophic adrenal gland was left undisturbed. Healing of the operative wound required four months. Three months after the operation, following preoperative preparation with whole and lipo-adrenal cortical extract, a right lumbar adrenal exploration was performed and a smooth encapsulated, yellowish-brown tumor about 3 cm. in diameter was removed. The pathological report was "fragment of adrenal gland with cortical adenoma of the adrenal." The postoperative course was stormy and marked by sudden episodes of shock, which gradually responded to the administration of adrenal cortical extract and parenteral fluids. Healing of the operative wound occurred after many months by secondary intention. Sixteen months postoperatively menstruation was regular, periorbital puffiness and facial hirsutism had disappeared, obesity was pronouncedly diminished, purpose striae were changed to white scars, blood pressure was normal, and the basal metabolic rate was +2%. Three years after operation the patient was in excellent health and asymptomatic. Successful surgical outcome in Cushing's syndrome caused by adrenal tumor depends on the type of underlying lesion as well as on the pre and postoperative management. It is now the author's policy to administer corticotropin (ACTH) preoperatively to stimulate the contralateral atrophic adrenal in spite of the risk of stimulating malignant tissue and of interfering with wound healing. Postoperatively both corticotropin and cortisone are concomitantly administered in order to stimulate the contralateral adrenal to produce adrenal cortical hormone and also to provide specific therapy in adequate dosage even if the adrenal cortical response to the pituitary fraction is inadequate. Later, cortisone and subsequently corticotropin are gradually withdrawn, thus permitting the endogenous production of corticotropin to be resumed.

Successful Repair of Accidental Transection of Penile Corpora.—Accidental complete transection of the penile corpora cavernosa and corpus spongiosum is reported in a 56-year-old man. Only the skin on the ventral aspect, the left side, and part of the right side of the penis joined it to the body. Transection occurred during the extension of a combined low hernial and upper scrotal incision. Under general anesthesia the two ends of the corpus spongiosum were coapted over an indwelling latex catheter. The sutures did not penetrate the mucosa. The septum pectiniforme of the corpora cavernosa was reconstructed and then the inner and outer layers of the tunica albuginea. Release of the clamp, which had initially been placed on the proximal corpora cavernosa at the discovery of the accident, gave a gush of blood which was controlled by further suturing of the tunica albuginea to effect a watertight anastomosis. The remaining wound was closed with black silk sutures. To prevent accidental removal of the catheter, it was anchored to the elongated prepuce with black silk. The penis was encased in ice to retard metabolism. Antibiotic therapy, sedation, and rigid catheter management were maintained with frequent inspection during the day for the cyanosis that would indicate gangrene. Slight temperature elevation, moderate hemorrhage from the operative site, and proximal penile edema occurred during the first few postoperative days. Pain sensation was found to be present in the glans on the second postoperative day. By the sixth day, the color of the penis generally had approached normal and the glans was quite sensitive to pinching. The sutures were removed. Because voiding was accompanied by slight escape of urine from the wound area, the catheter was kept in place until the twenty-first postoperative day, when the patient was discharged with only a minor seepage of urine from the operative site at each voiding. During the follow-up period the urethra was occasionally dilated to the diameter of a no. 22 French catheter. One and a half years after the accident the aberrant urinary stream had decreased to small drops which could be prevented by digital pressure. The patient's sexual life is perfectly satisfactory. His urethral caliber is adequate, although undetermined. Thus surgical and postoperative follow-up resulted in complete physiological rehabilitation. This is believed to be the first such case reported in the literature.

Peyronie's Disease Associated with Dupuytren's Contracture.—The combination of Peyronie's disease and Dupuytren's contracture is reported in 10 patients between the ages of 48 and 67. Penile induration and curvature was present in all patients. Pain on erection occurred in seven and some loss of potency in four. Both hands were involved by Dupuytren's contracture in eight, the right hand in one, and the left hand in another. Frequently the patients noticed that Peyronie's disease first became evident after abstinence from sexual relations. In about half of the patients trauma could have played a role in the etiology of both conditions, although in the other half this was not the case. Heredity could not be demonstrated as a predisposing factor. The patients were treated with 100 mg. of alpha-tocopherol three times daily for 6 to 12 months. No untoward effects from the administration of the drug were observed. Of the 10 patients, 4 improved greatly and 4 moderately. Two felt that there was some improvement in both conditions. Since most of the patients were benefited by the treatment with alpha tocopherol, the authors feel that further investigation with this method of treatment is justified.

Metabolism, New York

1:383-478 (Sept.) 1952

Significance of Lactescence in Blood Serum. W. F. Van Eck, J. P. Peters and E. B. Man.—p. 383.
Uptake of Fat by Adipose Tissue in Vitro. B. Shapiro, D. Weissmann, V. Bentor and E. Wertheimer.—p. 396.
Up to Four Decades of Hyperglycemia in Diabetics Without Loss of Carbohydrate Tolerance. H. J. John.—p. 400.
Excretion of Formaldehydogenic Steroids in Diabetics. S. M. Wolfe and K. E. Paschkis.—p. 413.
Time Course of Serum Copper Concentrations of Patients with Myocardial Infarctions. I. B. L. Vallee.—p. 420.
Questionable Significance of Ratios of Phosphorus, Nitrogen and Sulfur with Reference to Metabolic Studies in Man: Based on Effects of ACTH, Cortisone and Aureomycin. F. Homburger, C. D. Bonner and W. H. Fishman.—p. 435.

Michigan State Medical Society Journal, Lansing

51:938-1112 (Aug.) 1952

Goiter Prevention in Michigan: Results of 30 Years' Voluntary Use of Iodized Salt. J. K. Altland and B. E. Brush.—p. 985.
Three Cases of Cerebral Palsy: Electroencephalographic and Pathologic Correlation. H. R. Prentice, H. Sidney Heersma and J. M. Hammer.—p. 990.
Clinical Management of Axillary Tumors. J. MacGregor and E. T. Thieme—p. 999.
Osteitis Deformans: Familial Constitutional Hereditary Background as Etiological Factors. R. C. Moehlig.—p. 1004.
Drug Therapy of Hypertension. S. W. Hoobler.—p. 1008.
Post-Mortem Cesarean Section with Survival of Identical Twins. L. F. Tcter.—p. 1013.
Ovarian Cyst in Transverse Mesocolon: Report of a Case. M. O. Cantor and H. E. Kleinert.—p. 1015.
Toxoplasmosis: Clinical Discussion with Presentation of Three New Cases. J. R. Doty and N. L. Matthews.—p. 1018.
Medical and Case Work Approach to Epilepsy. C. A. Hakenen.—p. 1021.

Minnesota Medicine, St. Paul

35:813-900 (Sept.) 1952

Treatment of Convalescent Cardiac Patient. C. M. Kurtz.—p. 837.
Review of Poliomyelitis at Ancker Hospital from 1931 to 1951. F. G. Hedenstrom.—p. 842.
Immunization During First Year. G. B. Logan.—p. 845.
Practical Nurses and Homemakers for Rural Minnesota. K. Densford, J. O. Christianson and E. Taylor.—p. 847.
General Aspects of Eczema. F. T. Becker.—p. 850.
Evaluation of Food Allergy in Cause of Eczema. E. T. Ceder.—p. 853.
Occupational Aspects of Eczema. H. G. Ravits.—p. 855.
Treatment of Eczema. R. R. Kierland.—p. 858.
Antibiotic Therapy of Bacterial Endocarditis. II. Current Trends in Treatment of Subacute Bacterial Endocarditis. J. E. Geraci.—p. 861.
Liposarcoma of Transverse Mesocolon: Report of Case. H. B. Neel.—p. 867.
Value of Flat Plate (X-Ray) in Diagnosis of Acute Abdominal Conditions. E. C. Paulson.—p. 870.

Missouri State Medical Assn. Journal, St. Louis

49:653-714 (Aug.) 1952

Pathologic Aspects of Carcinoma of Stomach. M. B. Dockerty.—p. 653.
Surgery of Mitral Valvular Disease. B. M. Parker and R. Paine.—p. 658.
Stellate Ganglion Block in Treatment of Various Syndromes Encountered in Cardiovascular Disorders. H. W. Carle.—p. 663.
*Avoidance of Recurrent Hyperthyroidism: 20 Year Study. W. Bartlett Jr.—p. 667.
Cassette Seriograph, 14 by 17 Inch, for Aortography, Nephrography and Adult Chest Angiocardiography: Preliminary Report. A. E. Brodeur.—p. 670.
Some Uses of Female Sex Hormones. D. L. Sexton.—p 675.

Avoidance of Recurrent Hyperthyroidism.—Prior to 1933 Bartlett treated a patient who had toxic goiter with what was then regarded as the standard operation. This operation was erroneously referred to as subtotal thyroidectomy, because portions of each lobe, varying from one-eighth to one-third, were left behind, the amount depending on the severity of the hyperthyroidism, the size of the lobe, the age of the patient, and the presence or absence of gross nodules. This operation aimed to achieve two objectives: to cure the hyperthyroidism and yet leave enough thyroid tissue to prevent postoperative hypothyroidism. A rather large incidence of persistent or recurrent hyperthyroidism convinced the author that these two objectives are mutually exclusive. In 1,100 operations performed before 1933, the failure rate was between 5 and 10%, and so the author abandoned the partial thyroidectomy practiced until then in favor of a truly subtotal thyroidectomy, in which 1 gm. or less of goitrous tissue is left in each lobe. That amount is about the smallest that can be left in the tracheoesophageal groove and as a lining for a generous portion of the lateral capsule. Postoperatively, the euthyroid state must be maintained by daily administration of thyroid, which the author believes must be life long except in exceptional cases. Occasional failures to cure hyperthyroidism by primary thyroidectomy have occurred in the nearly 20 years that have elapsed since this change in treatment, but in each of these cases there had been an error in estimating the pathological situation. Radical, subtotal thyroidectomy, as carried out by Bartlett since 1933, will produce virtually complete and permanent cure of hyperthyroidism.

Nebraska State Medical Journal, Lincoln

37:273-308 (Sept.) 1952

Diagnosis and Surgical Treatment of Hirschsprung's Disease. O. Swenson.—p. 275.
Treatment of Severe Diabetic Acidosis. H. C. Lueth and H. V. Freidell.—p. 277.
Bilateral Thoracolumbar Sympathectomy in Treatment of Essential Hypertension. S. E. Potter.—p. 281.
Contact Dermatitis. A. C. Curtis.—p. 285.
Adenomyosis of Uterus. S. L. Wolters.—p. 290.
Pyuria in Children. J. M. Baty.—p. 293.

Neurology, Minneapolis

2:369-460 (Sept.-Oct.) 1952

Essential Mechanism in Myotonia: Electromyographic Study. W. M. Landau.—p. 369.
Cerebral Angiography in Diagnosis of Subdural Hematoma. J. M. Stein.—p. 389.
Hypnosis in Differentiation of Epileptic from Convulsive-like Seizures. J. W. Sumner, R. R. Cameron and D. B. Peterson.—p. 395.
Mesantoin in Control of Epilepsy. A. E. Loscalzo.—p. 403.
*Role of Food Allergy in Multiple Sclerosis. O. F. Ehrentheil, M. H. Schulman and L. Alexander.—p. 412.
Korsakoff's Psychosis Associated with Cerebral Tumors. B. E. Sprofkin and D. Sciarra.—p. 427.
What Has Neurology to Offer Child Guidance? A. R. Timme.—p. 435.

Food Allergy in Multiple Sclerosis.—This paper is concerned with 65 patients with clinically proved multiple sclerosis. The investigations included inquiry into a history of allergy, a dietetic analysis, examination of the nasal mucous membrane, skin testing by the scratch method with 15 common foods, plus tree, grass, and ragweed pollen extracts, and ophthalmic food tests with 25 common foods. In this last method the food proteins are incorporated into a bland ophthalmic ointment, of which a small amount is placed on the conjunctiva of the lower lid and allowed to dissolve. A positive ophthalmic reaction is characterized by hyperemia in one to four hours. Patients showing positive reactions were placed on a diet eliminating all foods that gave positive

ophthalmic reactions, or which the history suggested as allergenic, for at least three months. The most noteworthy observation was the high percentage of positive reactions to rye and wheat in the multiple sclerosis group, whereas rice elicited a reaction only once. This is significant in view of the high incidence of multiple sclerosis in countries where rye bread is one of the important foods and of low incidence in countries where rice is the daily food. Allergen-free diets brought about favorable therapeutic results in 31% of the cases. In 12 cases the temporary reintroduction of the previously omitted food resulted in temporary exacerbations of symptoms. An analysis of the dietary habits of a representative group of multiple sclerosis patients showed lack in calcium and iron in 50% of the cases, lack in fat in 24%, and lack of proteins in 31%, whereas in the diets of many of these patients there was a relative preponderance of carbohydrates. The authors admit that the opinion that food allergy plays a role in multiple sclerosis does not exclude the possibilities of a bacterial allergy, a virus etiology, or of a metabolic disorder. The favorable therapeutic response to the cereal-free diet may also be partly due to the reduction of the carbohydrate intake. A disturbance of the carbohydrate metabolism in multiple sclerosis is suggested by the work of Jones, who found an excessive amount of pyruvic acid in the blood of the severely ill patients. There is also the question whether the "subclinical" allergies found in the general population may gain relative importance in multiple sclerosis patients because of their vulnerable capillary system. Intercurrent infections, trauma, emotional upsets, or other stress often influences the course of multiple sclerosis adversely, and it is possible that allergic reactions may play a similar role.

New England Journal of Medicine, Boston

247:339-378 (Sept. 4) 1952

*Treatment of Endometriosis and Other Gynecologic Conditions with Large Doses of Estrogens. L. M. Hurxthal and A. T. Smith.—p. 339.
Acrodynia Following Ingestion of Mercurial Ointment: Late Dental Sequelae. F. N. Silverman and H. A. Cassady.—p. 343.
Therapeutic Application of Heat: Its Uses and Abuses. G. M. Piersol.—p. 346.
*Acute Appendicitis During Menstruation. A. A. Levi.—p. 350.
Diabetes Mellitus. S. B. Beaser.—p. 353.

247:379-418 (Sept. 11) 1952

Importance of Blood Groups in Laboratory and Clinical Medicine. F. H. Allen Jr.—p. 379.
Clinical Use of Nor-Epinephrine in Treatment of Shock Accompanying Myocardial Infarction and Other Conditions. G. S. Kurland and M. Malach.—p. 383.
Pulmonary Function in Convalescent Poliomyelitis Patients: III. Compliance of Lungs and Thorax. B. G. Ferris Jr., J. Mead, J. L. Whittenberger and G. A. Saxton Jr.—p. 390.
Adiposis Dolorosa (Dercum's Disease). W. A. Steiger, H. Litvin, E. M. Lasche and T. M. Durant.—p. 393.
Diabetes Mellitus. S. B. Beaser.—p. 397.

Estrogens in Endometriosis and Other Gynecologic Conditions.—Estrus-producing compounds were administered to 25 patients with endometriosis, 4 patients with uterine hemorrhages, 5 with fibroids, and 2 with chronic cystic mastitis. The various drugs used were diethylstilbestrol, "micronized (des) stilbestrol," dienestrol, and occasionally estrone sulfate. Doses varied from 5 to 50 mg. each day. Of the 25 patients with endometriosis, the condition was verified microscopically in 9, while diagnosis was made by the usual clinical criteria in the remaining 16. Temporary relief was obtained in most of them. Treatment was discontinued in seven patients for the following reasons: failure to relieve pain in four, development of a swollen labia in one, pronounced fluid retention and presumably congestive heart failure in another, and psychotic symptoms in a third patient. Estrus-producing compounds may be helpful in the treatment of endometriosis, but their usefulness is limited because of unpleasant side-effects or undesirable complications. In a few cases the results of treatment are highly satisfactory. Satisfactory results were obtained in eight patients with menorrhagia with and without fibroid and in the two patients with chronic cystic mastitis. Carcinoma of the breast occurred in two patients, one a diabetic who had been treated for menorrhagia associated with a fibroid tumor, and another who was treated for menorrhagia associated with the menopause. It is not believed that cancer of the breast is caused by estrogens, but if subclinical carcinoma is present, the growth may in some cases be accelerated. Diethylstilbestrol or other estrogens are useful in the temporary management of excessive uterine bleeding but probably should not be employed for an extended time in any case in which a definite family history of carcinoma has been obtained. In the authors' cases the nodules of chronic cystic mastitis and uterine fibroids decreased in size, but this observation must be substantiated by further clinical observations.

Acute Appendicitis During Menstruation.—Of 242 female patients between the ages of 11 and 50 on whom appendectomy was performed at three different hospitals by various surgeons, 24 were operated on during the menstrual period. Only 9 of these 24 patients had acute appendicitis, demonstrating the rarity of this condition during menstruation. The remaining 15 patients gave no evidence of acute appendicitis, and their records did not give a clear picture of the indications for surgical intervention; it seems that a longer waiting period and complete examination might have obviated these procedures. An illustrative case is reported in a 20-year-old girl with symptoms suggesting acute appendicitis at the start of her acute illness. These subsided in about 18 hours. Three days after her illness began, a ruptured left ovarian cyst, enlarged because of endometriosis, was removed at surgical intervention. The appendix was also involved with endometriosis. Both organs were treated surgically through a low midline incision. The ovary could not have been reached through a routine appendectomy incision, and another incision would have been necessary if the patient had been operated on when first seen. In this case the symptoms suggested acute appendicitis but were primarily due to pelvic disease, suggesting that vaginal or rectal examination during menstruation be performed when acute appendicitis is suggested. Furthermore, the authors believe that nearly all patients with acute symptoms in the lower abdomen and pelvic cavity during a menstrual period may safely be subjected to conservative treatment and continued observation. Thus needless operation for a "benign" appendix will be avoided during menstruation, and better surgical care of the patient for her chronic gynecologic disease will be permitted when the time for it has arrived.

New Jersey Medical Society Journal, Trenton

49:377-414 (Sept.) 1952

Obstetrical Emergencies. J. N. Connell.—p. 380.
Ossifying Fibroma of Ethmoid: with Case Report. A. Dintenfass, L. S. Ellenbogen and M. S. Ersner.—p. 386.
Polyposis of Large Bowel. P. Mecray Jr. and E. H. Kain.—p. 389.
Pregnancy and Diabetes. A. Ellis.—p. 392.
Some Chronic Pulmonary Disease Problems in General Practice. S. Cohen.—p. 396.
Psychiatrist's Role in General Hospital. D. H. Stephenson.—p. 399.
Diabetic Retinopathy: with Special Reference to Juvenile Diabetes. R. Siegel.—p. 402.
Diced Homologous Cartilage in Hernioplasty. G. F. Simms and R. C. Irwin.—p. 406.

New Orleans Medical and Surgical Journal

104:603-650 (Sept.) 1952

Interpretation of Serologic Test for Syphilis. R. H. Kampmeier.—p. 603.
Medullary Fixation of Fractures of Long Bones. R. H. Alldredge, D. C. Riordan and C. Harris.—p. 619.
Inguinal Hernia. W. Moss.—p. 631.
Recent Developments in Diagnosis of Renal Tumors. F. C. Hamm and H. C. Harlin.—p. 634.
Effects of Calcified Lymph Nodes Perforating Bronchial Tree. M. M. Ziskind.—p. 640.

North Carolina Medical Journal, Winston-Salem

13:457-536 (Sept.) 1952

New Frontiers of American Medicine. R. A. Moore.—p. 457.
Evaluation of Present Methods of Treatment of Prostatic Obstructions. W. M. Coppridge, L. C. Roberts and J. Hughes.—p. 463.
Use of Radioactive Iodine in Diagnosis and Treatment of Thyroid Disease. E. Yount, J. R. Andrews and A. W. Jester.—p. 466.
Gastrointestinal Diverticula with Emphasis on Diverticulosis and Diverticulitis of the Colon. P. A. Shelburne.—p. 470.
There Were Giants in Those Days: Evolution of Medicine in North Carolina. F. R. Taylor.—p. 479.
Accidental Administration of Dicyclomine (Bentyl) Hydrochloride in Overdosage: Report of Case with Recovery. A. R. Pittman Jr.—p. 486.

Oklahoma State Medical Assn. J., Oklahoma City

45:275-310 (Aug.) 1952

Some Current Thinking on Infantile Colic. L. L. Kishner.—p. 277.
Helping your Patient Accept Psychiatric Referral. H. J. Binder.—p. 279.
Preceptor Plan. R. H. Lindsay.—p. 283.
Emergency Treatment of Severe Head Injuries. H. L. Puckett.—p. 285.

Pediatrics, Springfield, Ill.

10:115-242 (Aug.) 1952

Growth of Thiocyanate Space in Infancy and Childhood. R. S. Ely and W. W. Sutow.—p. 115.
Prognosis of Palsies from Cranial Nerve Involvement in Poliomyelitis. H. U. Zellweger and E. Gabathuler.—p. 127.
*Tuberculosis of Cervical Lymph Nodes. O. Swenson and W. T. Small. —p. 131.
*Fulminating Meningococcemia Treated with Cortisone; Use of Blood Eosinophil Count as Guide to Prognosis and Treatment. H. L. Hodes, R. E. Moloshok and M. Markowitz.—p. 138.
Fat Disease of Liver in Infants on Isthmus of Panama. F. H. Howard and W. A. Meriwether.—p. 150.
Gumma of Stomach in Congenital Syphilis. G. Willeford, J. H. Childers and W. R. Hepner.—p. 162.
Congenital Familial Nonhemolytic Jaundice with Kernicterus. J. F. Crigler, Jr. and V. A. Najjar.—p. 169.
Reactivity of Skin of Newborn Infant. A. Matheson, M. Nierenberg and J. Greengard.—p. 181.
Combined Pelvic and Retroperitoneal Teratomas in Infancy and Childhood. E. E. Arnheim.—p. 198.
Glycogen Disease of Heart: Report of Two Cases Occurring in Siblings. A. W. Childs, R. F. Crose and P. H. Henderson.—p. 208.

Tuberculosis of Cervical Lymph Nodes.—The occurrence of cervical tuberculous adenitis, once a common disease but now a rare condition in the United States, is reported in 11 children between the ages of 22 months and 14 years. Three of these 11 patients were treated with streptomycin preoperatively. In two of these, the results were complete failures and required subsequent surgical intervention for control of the disease. One patient treated with streptomycin had a chronic draining sinus, a poor cosmetic result, and a recurrence. The prolonged series of painful injections was of some hazard and inconvenience to these patients. The chronic draining sinus in these patients was bothersome and probably dangerous because acid-fast organisms are usually present in the discharge. The 10 patients whose diseased lymph nodes were removed had good results; there were no recurrences and cosmetic results were satisfactory. One patient had slight drainage for three weeks, which was probably attributable to the fact that a drain was used in the wound. One patient whose diseased preauricular lymph node was incompletely removed had drainage in small amounts for three weeks. This demonstrates the importance of complete removal of all involved lymph nodes. Three patients had involvement of the preauricular nodes, which clinically could not be distinguished from a tumor of the parotid gland. Sialograms in two patients demonstrated the mass to be outside the parotid tissue. In none of these patients was there any postoperative evidence of nerve damage. The patients operated on were given 1 gm. of streptomycin daily for two weeks postoperatively. The results were not better than those reported by other authors without its use. Although the group of patients reported on is small, the results obtained suggest that surgical excision of the diseased lymph nodes is the best treatment for cervical tuberculous adenitis. Since the common route of infection of the cervical lymph nodes is by way of the tonsils or the adenoids, tonsillectomy and adenoidectomy should be performed on all patients with cervical tuberculous adenitis. If enlarged cervical lymph nodes are present two weeks after this intervention, they should be excised. Only in cases in which the skin is thin and red over the lymph nodes and spontaneous drainage is imminent should tonsillectomy be deferred until after excision of the lymph nodes. Streptomycin, which may fail as a sole therapeutic agent, may be of value as a postoperative adjunct to surgery.

Blood Eosinophil Count and Cortisone in Fulminating Meningococcemia.—The total blood eosinophil count was studied as an indicator of the adequacy of the adrenocortical response to the stress of acute infection in 8 children with acute meningococcus infection of mild or moderate severity and in 18 children with rubeola, pneumonia, or diphtheria. Pronounced eosinopenia was observed in seven of the eight children with acute meningococcus infection and in all of the patients with the other infectious diseases. During convalescence the number of eosinophils in the blood became normal. The eighth patient with mild meningococcus infection who was admitted during the recovery stage had a normal count, which decreased sharply after the administration of corticotropin (ACTH). In striking contrast with the uniformly low eosinophil levels in the children who recovered without difficulty from mild to moderately severe meningococcus infections, were the relatively normal levels in three children between the ages of 5 months and 11 years with fulminating meningococcemia. The authors felt that the absence of eosinopenia in these three patients might be considered as evidence of poor adrenocortical response. For this reason all three patients, in addition to usual forms of therapy, were treated with cortisone in an attempt at replacement therapy. One patient died shortly after admission, and the two other patients survived. It is believed that cortisone was of value in these latter two cases and that one of the patients would have certainly died without its use. Cortisone may prove to be of value in the treatment of fulminating meningococcus infection because it is much more potent in overcoming stress than previously employed adrenal extracts. It is suggested that the circulating eosinophil count may be of value as a guide in the prognosis and treatment of meningococcus infections.

Pennsylvania Medical Journal, Harrisburg

55:881-976 (Sept.) 1952

Earlier and More Complete Surgery in Ulcerative Colitis. H. W. Cave and S. Winslow.—p. 905.
Gallbladder Disease and Radiologist. C. L. Hinkel.—p. 910.
Differential Diagnosis of Rheumatic Fever in Children Without Aid of Advanced Laboratory Facilities. D. S. Polk.—p. 917.
Medical Conditions Simulating Acute Surgical Conditions in Abdomen. W. B. Gordon.—p. 921.
Recent Advances in Surgery of Adrenal Gland. H. A. Zintel.—p. 925.

Plastic & Reconstructive Surgery, Baltimore

10:67-148 (Aug.) 1952. **Partial Index**

Observations on Development of Circulation in Skin Grafts. IV. Effect of Corticotropin (ACTH) on Homologous Skin Grafts. H. Conway, R. B. Stark and D. Joslin.—p. 67.
Use of Bone-Bank Bone. L. W. Taylor and R. R. Kessler.—p. 72.
*Cleft Lip and Palate and Parental Age: Statistical Study of Etiology. W. G. McEvitt.—p. 77.
Secondary Repair of Unilateral Cleft Lip Deformity: Square Flap Technique. H. M. Trusler and S. Glanz.—p. 83.
New Technique for Harelip. A. D. Cardoso.—p. 92.
"Open" Method for Donor Site Dressing Using Waxed Paper. J. C. Weeter. —p. 96.
Split-Thickness Skin Grafting of Amputation Stumps. T. J. Canty and E. E. Bleck.—p. 99.
Correction of Internally and Externally Deviated Nose. E. D. King and F. L. Ashley.—p. 116.

Cleft Lip and Palate and Parental Age.—The cause of cleft lip and palate is still imperfectly understood. A century of study has eliminated superstitions and unwarranted assumptions, but a final answer to the problem is still being sought. Several observers, including the author of this report, were under the impression that the parents of children with cleft lip or palate were of greater than average age. To verify this, McEvitt made an analysis of 282 chronologically consecutive and unselected cases of cleft lip and palate listed in the files of the Straith Clinic. As a control group the birth registrations of the Detroit Health Department were tabulated. The comparative analysis of these two groups revealed that parental age had no bearing on the incidence of cleft lip and palate. The author briefly reviews other theories of the cause of cleft lip and palate, such as intrauterine trauma, dietary deficiencies of the mother, communicable disease, such as German measles, in the mother, but shows that none of these seem to have any bearing. The only causal factor for which there is evidence is heredity, but the incidence even among children of a deformed parent is not great, although it has been estimated at 20 times as common among the children of afflicted parents as in the general population. Any unborn child has about one chance in 750 of being born with a cleft lip or palate, but once the deformity appears the situation changes. In this case the gene is known to be present and the odds are possibly 50 to 1 that it will be present in the offspring. Parents should be assured that this deformity is not the result of wrongdoing on their part, that it is not caused by maternal impressions, or by

syphilis or any other known communicable disease. The young persons who have one afflicted child and hesitate to have another should be told that they still have statistically all of the odds in their favor. This is also true of the afflicted adult who is considering marriage, except in the case of marriage with another afflicted person.

Postgraduate Medicine, Minneapolis

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Diagnosis and Treatment of Hyperparathyroidism. R. W. Schneider. —p. 293.
Carcinoma in Rectal Polyp: Follow-Up Observations on 27 Patients. R. B. Turnbull Jr. and E. R. Fisher.—p. 303.
Treatment of Duodenal Ulcer. C. H. Brown and S. O. Hoerr.—p. 308.
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Management of Patients with Renal Lithiasis. C. C. Higgins.—p. 345.
Diseases of Gallbladder and Biliary Tract. S. O. Hoerr.—p. 353.

Psychiatry, Washington, D. C.

15:231-350 (Aug.) 1952. **Partial Index**

Effect of Brain Damage on Personality. K. Goldstein.—p. 245.
Problems in Determining Maternal Attitudes Toward Newborn Infants. D. M. Levy and A. Hess.—p. 273.
Successful Outpatient Psychotherapy of Chronic Schizophrenic with Delusion Based on Borrowed Guilt. A. T. Beck.—p. 305.

Public Health Reports, Washington, D. C.

67:829-928 (Sept.) 1952. **Partial Index**

*Morbidity and Mortality Experience Among Chromate Workers. H. P. Brinton, E. S. Frasier and A. L. Koven.—p. 835.
New Antituberculosis Drug? R. H. Anderson.—p. 848.
Food Supply and Emergency Feeding in Civil Defense. P. B. Murphy, L. R. Trainer and J. M. Hundley.—p. 860.
Necessary Foods for Emergency Feeding. J. M. Hundley.—p. 864.
Cancer Control in the United States. R. F. Kaiser.—p. 877.
Primary Isolation of Brucella from Human Blood Clots. S. R. Damon, D. Bunnell, K. Gay and L. M. Hutchings.—p. 883.
Practical Management of the Recalcitrant Tuberculous Patient. C. Northrop, J. H. Fountain and D. W. Zahn.—p. 894.
Coordinated Investigation of Food Poisoning Outbreak. F. A. Korff, M. Taback and J. H. Beard.—p. 909.
Kahn and Kolmer Tests for Syphilis. S. Olansky, A. Harris, F. G. Harb and others.—p. 923.

Morbidity and Mortality Among Chromate Workers. — In 1950-51 the Public Health Service made an engineering study of the working environment in all seven chromate-producing plants in the United States, and a detailed medical study of workers in six of these plants. Data were collected on death claims and on claims for sickness and injuries disabling for eight days or longer. Sickness among these chromate workers was compared with that of other industrial workers. The chromate workers had sickness rates that, except for cancer, were not greatly different from those of other workers. Their cancer rate of 7.1 compared with 0.7 for workers in other industries stands out, however. During the nine-year period 1940-48, the average annual death rate per 100,000 males aged 15 to 74 years was 1,503.1 for chromate workers and 927.8 for the corresponding male population of the United States; if cancer was disregarded the figures were 923.6 and 797.5, respectively. The number of deaths of chromate workers from all cancers was approximately four and one-half times that of the cancer death rates for all males in the United States, but it was 29 times as great when cancer of the respiratory system was considered separately. Deaths from all other types of cancer failed to show an excess among chromate workers.

Review of Gastroenterology, New York

19:611-664 (Aug.) 1952

Refractory Peptic Ulcer. J. B. Kirsner, E. Levin and W. L. Palmer —p. 611.
Indications for Vagotomy in Surgical Treatment of Patient with Chronic Peptic Ulcer which has Failed to Respond to Medical Management E. M. Miller.—p. 624.
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Mesenteric Vascular Occlusion. B. J. Ficarra.—p. 656.
Treatment of Diarrheal Syndrome with Resion. H. K. Gabroy and S. Horoschak.—p. 660.

Rhode Island Medical Journal, Providence

35:421-460 (Aug.) 1952

Present Status of Adreno-Cortical Hormone Therapy, Its Uses and Limitations. J. L. Bakke.—p. 421.
Cardiac Surgery. H. B. Shumacker Jr.—p. 439.

Rocky Mountain Medical Journal, Denver

49:663-720 (Aug.) 1952

Esophageal Hiatus Diaphragmatic Hernia. S. W. Harrington.—p. 665.
Surgery of Benign and Malignant Tumors of Skin and of Head and Neck H. Conway.—p. 673.
Unusual Anomaly of Cystic Duct. C. A. Hager.—p. 678.

49:745-800 (Sept.) 1952

Return to Medicine. P. R. Holtz.—p. 747.
Psychiatric Approach to Patients with Malignant Disease. C. H. H. Branch —p. 749.
Treatment of Certain Recalcitrant Skin Diseases with Thorium X. H. M Lewis, G. M. Frumess and E. J. Henschel.—p. 753.
Myasthenia Gravis—Diagnosis and Treatment. F. B. Walsh.—p. 757.

South Dakota J. Med. & Pharmacy, Sioux Falls

5:181-202 (July) 1952

Surgical Management of Varicose Veins. H. G. Scott.—p. 181.
Infant Feeding. S. L. Arey.—p. 188.

Southern Medical Journal, Birmingham, Ala.

45:779-884 (Sept.) 1952. **Partial Index**

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Results of Lobotomy in Mental Disorders. J. G. Lyerly.—p. 793.
*Viral Hepatitis Following Use of Ultraviolet Irradiated Human Plasma J. L. Thompson Jr. and W. D. Sutliff.—p. 801.
Problems in Anesthesia for Intestinal Obstruction. R. B. Dodd.—p. 805.
Management of Injuries of Urethra and Genitalia. J. Hyman.—p. 810.
Intramedullary Fixation of Fractures of Forearm. R. H. Hall, E. I. Bugg and R. E. Vitolo.—p. 814.
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Responsibilities and Facilities Available in Private Neuropsychiatric Hospital to Medical Profession. A. J. Schwenkenberg, J. L. Knapp and J. C. Powell Jr.—p. 844.
The Hospital's Training Program in Relation to the Medical School B. I. Burns.—p. 849.
Life Cycle of the Allergic Individual. C. M. Pounders.—p. 857.
Acute Agranulocytosis During Use of Tibione®: Report of Case. J. A Davis, A. J. Viehman and W. B. Frommeyer Jr.—p. 861.
*Tung Nut Poisoning. E. Balthrop.—p. 864.
Critical Analysis of Young and Elderly Primiparas. J. M. Nokes, W. N. Thornton Jr. and T. C. King Jr.—p. 866.
Treatment of Nonspecific Urinary Infections. W. L. Bush.—p. 870.

Viral Hepatitis Following Use of Ultraviolet-Irradiated Plasma. —It had been assumed that the hazard of transmission of hepatitis by plasma had been eliminated by the irradiation of plasma with ultraviolet rays. When reports continued to appear, however, indicating that hepatitis developed despite such irradiation, Thompson and Sutliff decided to investigate the incidence of viral hepatitis occurring after infusions of irradiated plasma, nonirradiated plasma, whole blood and combinations of the two types of plasma with whole blood. The records in 182 cases of viral hepatitis occurring in a Veterans Administration Hospital between 1947 and 1951 were reviewed. There was evidence that blood or plasma or both had been administered from one to six

months before onset of hepatitis in 39 of these cases. Four cases of viral hepatitis occurred following the administration of irradiated plasma alone and four cases occurred following the administration of irradiated plasma and whole blood. These cases are described. Three cases of viral hepatitis followed the infusion of nonirradiated plasma, eight cases followed the infusion of such plasma plus blood and 20 cases followed the use of blood alone. The authors deduce from this that the substitution of ultraviolet-irradiated plasma for nonirradiated plasma reduced but did not entirely prevent the development of viral hepatitis.

Tung Nut Poisoning.—The tung nut tree, Aleurites fordii, which originated in China, is of great importance for the paint industry, because its oil constitutes a valuable drying agent. This tree was introduced into the United States in 1932 and now constitutes an important agricultural crop in many of the southern states. The toxic nature of tung nuts had been known for a long time, but efforts to isolate the toxic material have not been successful as yet. It has been suggested that the toxicity is related to the protein, or that there is a lipid fraction that is toxic. At a hospital in Mobile, Ala., 10 cases of poisoning with tung nuts were observed. All but one of the patients were children. Gastroenteritis, as evidenced by nausea, vomiting, diarrhea, cramps, and thirst, was present in all cases, and these symptoms may progress to serious fluid and electrolyte deficiency. Cyanosis, paresthesias, mydriasis, irregular respirations, and reflex changes occur in some cases. There may also be temporary renal dysfunction, resulting in glycosuria, crystalluria, concentration, and casts. The similarity of the toxic effects produced by tung nuts to those of atropine suggest the possibility of pilocarpine as an antidote, but symptomatic treatment is highly successful. Gavage is unnecessary, because of vomiting. Replacement of fluid and electrolytes is probably most important, but central nervous system depression may demand primary consideration. Magnesium sulfate may be a specific antidote, either as an osmotic diluent of the toxic material in the gastrointestinal tract or as a detoxifying agent, since proteins are denatured by the sulfate ion.

Surgery, Gynecology and Obstetrics, Chicago

95:257-312 (Sept.) 1952

Inefficient Uterine Action. T. N. A. Jeffcoate, K. Baker and R. H. Martin.—p. 257.
Ascorbic Acid in Surgical Patients with Particular Reference to Their Blood Buffy Layer. I. Survey of Blood and Tissues. J. H. Crandon, S. Mikal and B. S. Landau.—p. 274.
Congenital Malformations of Rectum and Anus II. Associated Anomalies Encountered in a Series of 120 Cases. T. C. Moore and E. A. Lawrence.—p. 281.
Results of Treatment of Fractured Mandibles by Anderson Splint. M. Stein, M. N. Teubes and S. Sher.—p. 289.
Congenital Hernia of Diaphragm with Special Reference to Right-Sided Hernia of Liver and Intestines. E. E. Arnheim.—p. 293.
Repair of Diaphragmatic Defects with Cutis Grafts: Experimental Study. E. D. Geever and K. A. Merendino.—p. 308.
Need for Adequate Aftercare in Complete Rehabilitation of the Disabled. A. P. Aitken.—p. 317.
*Diagnosis, Treatment, and Prophylaxis of Potassium Deficiency in Surgical Patients: Analysis of 404 Cases. H. S. Lans, I. F. Stein Jr. and K. A. Meyer.—p. 321.
Hypotensive Spinal Anesthesia. N. M. Greene.—p. 331.
Surgical Treatment of Varicose Veins in Pregnancy. F. W. Quattlebaum and J. E. Hodgson.—p. 336.
Local Recurrence Following Subtotal Resection for Gastric Carcinoma. F. B. Thomson and R. E. Robins.—p. 341.
*Spontaneous Rupture of Esophagus: Experimental and Clinical Study. S. A. Mackler.—p. 345.
Phylogenetic Study of Recurrent Anterior Dislocation of Shoulder Joint. J. A. Dickson and H. W. O'Dell.—p. 357.

Potassium Deficiency in Surgical Patients.—This report on potassium deficiency is based on observations on 404 surgical patients studied during a 12-month period at the Cook County Hospital. The authors consider the normal range of serum potassium to be between 4.0 and 5.6 mEq. per liter, and say that 309 of their patients had a serum potassium below 3.7 mEq. per liter. Of 241 patients who had potassium deficiency preoperatively, 160 had hypopotassemia on admission. Fourteen who had a normal serum potassium on admission were found to have a hypopotassemia following correction of severe dehydration by parenteral administration of fluids. Sixty-seven patients had a hypopotassemia after varying periods of hospitalization. All these patients had been treated with potassium-free fluids since admission, and all but nine had been subjected to gastric suction drainage. In 69 patients persistent hypopotassemia developed postoperatively. Potassium deficiency in surgical patients was traced to limitation of potassium intake, prolonged parenteral use of potassium-free solutions, loss of gastrointestinal secretions, increased renal excretion of potassium resulting from surgical trauma, diuresis due to infusions of large amounts of sodium chloride or glucose solutions, and disturbances in acid base balance. The use of gastrointestinal suction drainage, without adequate replacement of potassium, was shown to lead to potassium deficit after four or five days. Muscular weakness was the commonest clinical finding. Anorexia, mental depression, and abdominal distention were also common. Hypochloremic alkalosis was frequently observed. Prophylactic use of potassium salts was studied in 90 patients, and the authors recommend it for patients with losses of gastrointestinal secretions due to suction drainage or fistulas; for patients receiving only parenteral alimentation for periods longer than four days; and for many patients undergoing extensive surgical procedures. Prophylaxis should begin when Levin suction and administration of intravenous fluids are started before operation and should be reinstituted 24 hours postoperatively and continued until a liquid diet is tolerated. Treatment of potassium deficiency is often essential for the survival of a patient. Administration of potassium salts must be done cautiously, however, and only under proper laboratory and clinical supervision. Concentrated solutions or rapid administration may cause heart block and cardiac arrest. The authors recommend for general use a solution containing 3 gm. of potassium chloride (40 mEq. of potassium) in a liter of fluid, which should be administered not faster than 120 to 180 drops per minute. Potassium must be administered very cautiously to patients with renal insufficiency or dehydration.

Spontaneous Rupture of Esophagus.—Spontaneous rupture of the esophagus is an uncommon accident, which occurs, in most instances, following prolonged or forceful vomiting. The rupture is characterized by a sudden splitting apart of the wall of an apparently normal esophagus with the escape of gastric content into the mediastinal space. Other acts which have resulted in rupture are straining at defecation, lifting a heavy weight, a convulsion seizure of grand mal epilepsy, and the labor of childbirth. Distinction is made between rupture and perforation of the esophagus. Perforation, except when produced by direct trauma, usually instrumentation, is the end result of a disease process involving the wall of the organ during which there is constant and progressive erosion. The perforation appears as a small, round hole and shows no predilection of site as to the circumference or axis of the esophagus. In contrast to perforation, rupture occurs as an abrupt tear in an apparently undiseased esophagus. The triad of vomiting, low thoracic pain, and emphysema of the neck is diagnostic of rupture and constitutes sufficient evidence to warrant a left thoracotomy. Evidence is presented to support the conclusion that rupture occurs in a previously normal, healthy esophagus as a result of intraesophageal pressure, transmitted from the stomach. The rupture uniformly occurs at the lower extremity of the esophagus upon the left lateral wall, apparently the weakest part of the organ. That this is indeed the weakest part of the esophagus was confirmed by experimentally inflating and bursting the esophagus of 65 fresh human cadavers. The site and configuration of the resulting rupture duplicated exactly the clinical lesion. Three cases of spontaneous rupture of the esophagus are described. The treatment consisted of left thoracotomy, suture of the esophagus, and drainage. The recovery of 2 of the patients brings to a total of 13 those surviving a spontaneous rupture of the esophagus. The outcome was uniformly fatal before the adoption of a surgical method of treatment.

West Virginia Medical Journal, Charleston

48:217-246 (Aug.) 1952

A Doctor of Medicine Interprets His Role as a Citizen in Our Democracy. S. S. Hall.—p. 217.
Slow Technique for Cerebral Angiography. W. A. Shafer.—p. 226.
Hematuria in the Traumatic Patient. J. G. Zekan.—p. 229.
Treatment of Complications of Peptic Ulcer. F. L. Coffey and G. F. Woelfel.—p. 232.

FOREIGN

Acta Chirurgica Scandinavica, Stockholm

103:241-320 (No. 4) 1952. **Partial Index**

*Liver Resection in Primary Malignant Hepatoma. T. G. Nyström.—p. 241.
Colon Transposition in Total Gastrectomy. R. Carleson and Y. Edlund. —p. 249.
Method of Direct Measurement of Blood Loss During Surgical Operations. I. Engdahl and H. Møller.—p. 258.
Mucus-Secreting Tumors of Jaws. J. Hertz.—p. 276.
Arthrography as Diagnostic Aid in Lesions of Knee Joint. S. B. Jensen and P. T. Andersen.—p. 302.

Liver Resection in Primary Malignant Hepatoma.—While the removal from the liver of solitary cysts and benign tumors has been considered feasible, resection of the liver for malignant tumors has been considered extremely risky. Opinions have changed, however. There have been reports that patients have survived for months or years after removal of solitary liver metastases in connection with extirpation of the primary tumor. This changed attitude is explained not only by the great improvement in the technique of liver resection but also by advances in anesthesiology and more effective pre and postoperative treatment. For successful removal of primary carcinoma of the liver a combination of especially favorable circumstances is required. The tumor must be recognized before its rapid spread; the liver function must be good; the cancer must be of the solitary hepatoma type; and resection must be made in healthy tissue, at a safe distance from the growth, without damage to vital structures. All these requirements were met in a case of primary carcinoma of the liver described in this paper. The patient, a woman, aged 64, is still alive and well 18 months after resection of the tumor.

Archiv für Kinderheilkunde, Stuttgart

145:1-96 (No. 1) 1952. **Partial Index**

Antibiotics and Chemotherapy in Children with Tuberculosis. O. Bossert, F. Dude and A. Massenberg.—p. 3.
Use of Conteben (Amithiozone) in Children. G. Proske.—p. 27.
Functional and Anatomic Changes in Pancreas in Leiner's Desquamative Erythroderma. A. Mester, M. Radek and L. Kadas.—p. 59.
Present Status of Scarlet Fever Endocarditis: Treatment and Prognosis. D. Lachemann.—p. 66.
*Aniline Poisoning in 41 Infants Caused by Laundry Inks. H. Rodeck and H. Westhaus.—p. 77.

Poisoning from Laundry Marking Ink in Infants.—Diapers and other clothing freshly marked with inks containing aniline dyes were used on 77 infants born at term and 29 prematurely born infants. Symptoms of poisoning developed in 20 of the prematurely born infants and in 21 of the full term infants, all of whom were less than three months old. According to the directions for use of the ink, it was to be applied very thinly with a pen; the marked diapers were not to be stacked one on top of the other, heated or ironed, but were to be exposed from one to three days and then washed. The laundry allegedly had followed the instructions except for the marking, which had been done with a broad-surfaced stamp. The ink contained an aniline salt, which by oxidation with potassium chlorate, bichromate, or iron compounds is transformed almost completely into the nontoxic aniline black. The outstanding symptom presented by the infants was cyanosis, which was of a grayish-brown rather than a blue tint. Most of the infants appeared tired and fatigued and muscular tonus was decreased. The pulse became weak and rapid so that circulatory stimulants had to be given. The respiratory frequency was increased. In some infants the reflexes were abolished temporarily, and some had anorexia so that they had to be tube-fed. The blood had a brownish to a blackish-brown color. The hemoglobin and erythrocyte values decreased within the first three days after poisoning to nearly 50% of the previous values. Absorption of the toxic dye was probably favored by the delicacy of the skin. Therapy consisted chiefly of blood transfusions, exchange transfusions being employed in some of the seriously ill premature infants. The children also were given intravenous injections of 2 to 4 cc. of calcium thiosulfate at eight hour intervals; presumably methylene blue could have been administered with the same effect. Cyanosis disappeared, and the color of the blood was normalized rapidly. Aside from secondary anemia and enlargement of the liver in a few of the infants, there were no late sequelae. The authors also describe animal experiments carried out with the toxic ink. They warn against the use of laundry inks that contain aniline dyes.

British Journal of Cancer, London

6:99-214 (June) 1952. **Partial Index**

Endemiology of Cancer of Lung in England and Wales. P. Stocks.—p. 99.
One Hundred Consecutive Primary Epithelial Lung Tumours. L. Kreyberg. —p. 112.
Neoplastic Disease Occurring in Varicose Ulcers or Eczema: Report of Six Cases. W. Black.—p. 120.
Adenocarcinoma of Oesophagus and Ectopic Gastric Mucosa. B. C. Morson and J. R. Belcher.—p. 127.
Cancer and Essential Hypertension. S. G. Zondek.—p. 131.
Catalase Poisons in Relation to Changes in Radiosensitivity. E. Boyland and E. Gallico.—p. 160.
Comparison of Cytological Effects Induced by X Rays and Nitrogen Mustard. P. C. Koller and A. Casarini.—p. 173.
Antimitotic Action of Aromatic Nitrogen Mustard on Tissue Cultures. L. M. Rinaldini.—p. 186

British Journal of Ophthalmology, London

36:465-528 (Sept.) 1952

Observations on Choroidal Circulation. N. Ashton.—p. 465.
Hexamethonium and Glaucoma. A. J. Cameron and R. A. Burn.—p. 482.
Vitreous Cyst with Retinitis Pigmentosa. A New Syndrome? J. W. Wagenaar.—p. 492.
Clinical Method of Observing Changes in Rate of Flow of Aqueous Humour in Human Eye. II. In Glaucoma. D. Langley and R. K. MacDonald.—p. 499.
Optic Atrophy with Altitudinal Hemianopia in Neurofibromatosis. B. Sheehan.—p. 506.
Measurement of Resistance to Aqueous Flow by Electronic Tonometer: Results in Cases of Congestive Glaucoma Before and After Treatment. R. Weekers and E. Prijot.—p. 511.
Cyclodialysis Combined with Posterior Trephining. H. J. Flieringa. —p. 518.

British Medical Journal, London

2:525-574 (Sept. 6) 1952

Dynamics of Heart Failure. J. McMichael.—p. 525.
Pathogenesis of Simple Goitre: Review. A. W. Spence.—p. 529.
Acute Circulatory Failure During Surgical Operations. J. F. Dark, T. Dinsdale, A. N. Guthkelch and L. P. Lassman.—p. 533.
Electric Convulsion Therapy in Treatment of Prolonged Stupor. P. H. Mitchell.—p. 535.
Cortisone and Tumour Growth. H. N. Green and H. J. Whiteley.—p. 538.
Absence of Response to Cortisone. G. D. Kersley, L. Mandel and M. H. L. Desmarais.—p. 540.
*Attempt to Prevent Erythroblastosis Foetalis by Use of Cortisone During Pregnancy. J. R. Anderson, G. M. Barr and A. Slessor.—p. 542.
Routine Use of Liquid Urea Medium for Identifying Salmonella and Shigella Organisms. L. G. C. Maslen.—p. 545.

Cortisone to Prevent Erythroblastosis Fetalis.—An Rh-negative woman with a high titer of Rh-incomplete antibody in her serum was seen at an early stage of her third pregnancy. The antibody titer remained at a high level throughout pregnancy. The husband of the patient was probably homozygous Rh-positive, and the previous infant, born two and one-half years ago, had died of erythroblastosis fetalis in spite of simple transfusion. From these considerations it seemed probable that the present pregnancy would result in intrauterine death or in an infant severely affected by erythroblastosis fetalis. To prevent this the patient was given a course of cortisone therapy from the 34th to the 37th week of the pregnancy, inclusive. Immediately after this the pregnancy was terminated. No harmful effect of cortisone therapy was observed in the mother. The infant was mildly affected by erythroblastosis fetalis and remained well following an exchange transfusion. The authors feel that this result is encouraging enough to warrant further trials of cortisone therapy. They discuss the criteria for the selection of suitable cases, and also the dosage and duration of such therapy. Details as to how the mother is to be protected against possible ill effects of cortisone are described.

Canadian Medical Association Journal, Montreal

67:183-288 (Sept.) 1952

Punishment and Maladjusted Child. R. W. B. Ellis.—p. 209.
Heterogeneous Sources of Neurology. F. Turnbull.—p. 217.
Injuries to Genito-Urinary Tract. J. T. MacLean.—p. 220.
*Liver Dysfunction in Chronic Alcoholics. Y. Rouleau and G. Nadeau. —p. 231.
*Curare-Like Factor in Serum of Myasthenia Gravis Patients. H. Schwarz. —p. 238.
Uncommon Abdominal Contingencies. R. K. Magee.—p. 245.
Control of Staphylococcal Skin Infections in Nursery. C. D. Farquharson, S. F. Penny, H. E. Edwards and E. Barr.—p. 247.
Chloromycetin and Chronic Ulcerative Colitis. D. L. McNeil.—p. 250.
Clinical Report on Use of Testosterone in Psychiatric Syndromes. E. L. Margetts.—p. 251.

Liver Dysfunction in Chronic Alcoholics.—Chronic alcoholics were subjected to various tests in an effort to determine the connection between liver dysfunction and chronic alcoholism. The subjects came from different classes of society and their alcoholic history covered from 2 to 30 years. Wines, whiskies, gin, ales, and liqueurs were among the alcoholic beverages consumed, but none of the patients was addicted to pure alcohol or related beverages, such as brandies, exclusively. A few patients showed mental disorders (acute hallucinatory psychosis, delirium tremens, and Korsakoff's psychosis) and some had gastric disorders. Renal function and cerebrospinal fluid were normal in every case. The study included a group of normal nonalcoholic controls. The primary function of the liver following alcohol ingestion is detoxification; consequently functional impairment could best be detected by such tests as the sulfobromophthalein (bromsulphalein®) retention test, the hippuric acid excretion test, and the Van den Bergh test. The results showed that sulfobromophthalein retention was definitely higher among the heavy drinkers. All chronic alcoholics after a few years show a similar type of liver dysfunction, that is, a failure in detoxifying ability varying in intensity from patient to patient. This pathological condition is apparently a kind of fatty degeneration and should not be confused with portal cirrhosis. The influence of the secondary constituents accompanying ethyl alcohol in alcoholic beverages has not yet been fully investigated, but many of them are known to be highly toxic and their effect on the liver cannot be assumed to be innocuous. Liver dysfunction in chronic alcoholism ultimately becomes irreversible, but there is a long period during which it can be successfully treated. Recent experiments have demonstrated the regenerating power of lipotropic substances, which impede the fatty degeneration preceding true cirrhosis. These substances were administered orally to the authors' patients in capsules containing 500 mg. of DL-methionine, 100 mg. of choline, 10 mg. of cystine, and 100 mg. of inositol, with 10 mg. of thiamine, 3 mg. of riboflavin, 3 mg. of pyridoxin, and 2 mg. of nicotinamide. Twelve capsules were given daily for from three to six weeks and the results were better than when dietary measures alone were used. Organic improvement was accompanied in many cases by mental improvement.

Curare-like Factor in Myasthenia Gravis. — Experiments were conducted to determine the effect on normal subjects of a transfusion with blood from patients with temporarily untreated myasthenia gravis and an intramuscular injection of myasthenic serum, as well as the effect on a patient with myasthenia gravis of a large and fairly rapid exchange transfusion with normal blood. Two patients with severe myasthenia gravis were chosen as donors for the first experiment, their blood and Rh groups corresponding to those of the nonmyasthenic recipient. No harmful effects resulted from the transfusion and no change occurred in the muscle strength of the recipient, as shown by repeated tests with a dynamometer. Daily observations of the recipient was continued for a week following the transfusion and then, as no undesirable manifestations were noted, the experiment was repeated, again without any harmful effect or any change in muscular strength. Next the normal subjects were tested for serum sensitivity, following which they received intramuscular injections of myasthenic serum in one forearm and an equal quantity of normal serum in the other forearm. The subjects did not know into which arm the myasthenic serum was given. Comparison of the dynamometric recordings taken before and afterwards showed that myasthenic serum induced abnormal muscular fatigue in the arm into which it was injected; normal serum had no such effect. A further test, made by injecting prostigmine into the arm weakened by myasthenic serum, resulted in prompt and dramatic recovery of strength. The third experiment, in which a myasthenic patient received an exchange transfusion of 4,000 cc. of fresh blood, showed that the procedure was not only not beneficial but that if anything the patient was made temporarily worse and required more prostigmine than usual.

Journal of Endocrinology, London

8:187-274 (July) 1952. **Partial Index**

Ovarian Control of Hypophysial Gonadotrophic Function. S. Bruzzone, A. Lipschütz and L. Niedmann.—p. 187.
Effect of High Doses of Ascorbic Acid on Functions of Adrenal Glands. S. Kayahan.—p. 211.
Effect of Hypothyroidism on Guinea-Pig. E. M. Humphreys.—p. 229.
Comparison of Plasma Inorganic Phosphate Levels in Normal and Diabetic Pregnancies. M. E. Morgans.—p. 242.
Effect of Exogenous Thyroxine on Radio-Iodine Uptake in Normal Subjects and in Cases of Thyrotoxicosis in Remission. M. E. Morgans, A. K. Oldham and W. R. Trotter.—p. 250.
Relaxation of Pelvis in Guinea-Pigs Following Implantation of Pituitary Glands. F. E. Emery.—p. 254.
Studies on Metabolism of Adrenal Steroid Hormones. J. A. Nissim. —p. 257.

Journal of Neurol., Neurosurg. & Psychiatry, London

15:143-218 (Aug.) 1952.

Observations on Partial Removal of Post-Central Gyrus for Pain. W. Lewin and C. G. Phillips.—p. 143.
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Thermal Sensation in the Bladder. P. W. Nathan.—p. 150.
Two Cases of Aspergillus Infection of Central Nervous System. S. Iyer, P. R. Dodge and R. D. Adams.—p. 152.
Localization of Aneurin Pyrophosphatase in the Brain. D. Naidoo and O. E. Pratt.—p. 164.
Wounds of Visual Pathway. II. Striate Cortex. J. M. K. Spalding. —p. 169.
Dysphasia in Left-Handed Patients with Unilateral Brain Lesions. M. E. Humphrey and O. L. Zangwill.—p. 184.
Cerebral Dominance in Cases of Reading Disability. J. McFie.—p. 194.
Electromyographic and Endocrine Studies in Chronic Thyrotoxic Myopathy. K. V. Sanderson and W. R. Adey.—p. 200.
Observations on Case of Myotonia Paradoxa. J. Marshall.—p. 206.
Vital Staining of Muscle Biopsies with Methylene Blue. C. Coërs.—p. 211.

Lancet, London

2:393-446 (Aug. 30) 1952

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Medical Education in America. R. Cruickshank.—p. 394.
Education by Travel. R. Whitehead.—p. 396.
Tuberculosis in Medical and Dental Students: Study at Guy's Hospital. A. B. Shaw.—p. 400.
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Selection of Medical Students: Experiences at University College, London. J. T. Aitken and M. L. Johnson.—p. 409.
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2:447-494 (Sept. 6) 1952

Dangers of Chronic Inactivity in the Aged. M. Hill.—p. 447.
Conversion of Tissue Polysaccharides to Auto-Antigens by Group-A Beta-Haemolytic Streptococci. L. E. Glynn and E. J. Holborow.—p. 449.
*Deforming Factors in Early Stage of Poliomyelitis. G. P. Mitchell. —p. 451.
Salt-Losing Nephritis. C. L. Joiner and M. G. Thorne.—p. 454.
Condition of Kidneys in Salt-Losing Nephritis. J. B. Enticknap.—p. 458.
*Retardation of Growth Associated with Hirschsprung's Disease. F. A. R. Stammers and A. J. H. Rains.—p. 461.
Treatment of the Adrenogenital Syndrome with Cortisone D. Hubble. —p. 464.
Thiopentone Followed by Nitrous Oxide and Oxygen for Anaesthetising Outpatients. E. H. Franks.—p. 466.
Tetraethyl Lead Poisoning: Report of a Non-Fatal Case. G. Walker and P. R. Boyd.—p. 467.

Deforming Factors in Early Stage of Poliomyelitis. — Mitchell applies the term deforming factors to any conditions that interfere with the passive mobility of the extremities in the early stage of poliomyelitis. His observations were made on over 100 patients. Deforming factors produce three outstanding signs: (1) limitation of straight leg raising; (2) limitation of shoulder abduction beyond 80 degrees; and (3) muscle resistance to stretch. The limitation of straight leg raising is that persisting after the initial acute meningeal reaction has subsided. When present, it

persisted for many weeks and could not be completely abolished by treatment in the early stage, but improved in the later stages on mobilization of the patient, particularly by walking and sitting. The limitation of straight leg raising was always bilateral, but was not present unless there was some paralysis of the leg. Limitation of shoulder abduction was a feature in the few patients presenting severe degrees of resistance to muscle stretch in the biceps and shoulder adductor muscles. Pain was produced on abduction beyond 80 degrees accompanied by strong resistance in the shoulder adductor muscles when these were active. Muscle resistance to stretch was characterized by sustained tone or "spasm" in the muscles of the neck and back during the meningeal reaction of the first few days. This sustained tone disappeared as the fever subsided, but was sometimes followed by muscle resistance to stretch, which developed on attempted flexion of the spine but gradually subsided. On the basis of clinical observations Mitchell concludes that the limitation of straight leg raising and shoulder abduction is due to pain arising from residual inflammatory changes in the region of the dorsal roots or meninges. In these cases muscle resistance to stretch is a guarding mechanism. The greater resistance to stretch found occasionally in muscles such as the biceps cannot be explained by a guarding action alone. Muscle incoordination plus overactivity due to emotion of a strong or relatively unaffected muscle over a weaker affected muscle may exaggerate the underlying guarding mechanism. The author agrees with Magoun and Rhines that further investigation of the pathophysiology of spasm in poliomyelitis is necessary before it can be stated definitely to be either an exaggerated stretch reflex or tension maintained reflexly or voluntarily in response to pain or to have some as yet unknown etiology.

Retardation of Growth Associated with Hirschsprung's Disease.—Surgical textbooks have pointed out that there are two types of megacolon, one in which dilatation and hypertrophy extends from the anus upwards and another in which various lengths of the rectum appear normal. In this second type Bodian and others demonstrated an abnormality of Auerbach tissue in the seemingly normal portion of the rectum, namely, absence of ganglion cells and some increase in size of the nerve fibers. It has been suggested that the term congenital megacolon should be restricted to this second type. The authors present the detailed history of a patient in whom vomiting and intestinal obstruction appeared at the age of 11 days; from then on he had recurrent attacks of obstruction and at the age of 3 years Hirschsprung's disease was diagnosed. Presacral sympathectomy and section of the lumbar colonic nerve produced no permanent relief, although there was some improvement, and because of this and of the war he was lost sight of until he was 18 years old. At this time he appeared more like a child of 10 years; his voice had not changed, his genitalia were underdeveloped, and he had no pubic or axillary hair. His abdomen was opened in July, 1949. Gross hypertrophy and dilatation of the ascending, transverse, descending, and sigmoid colon were found. The mesocolon and mesosigmoid were enormously thickened. At the rectosigmoid junction the bowel narrowed and appeared constricted. Colectomy seemed contraindicated by the patient's poor condition. It was suggested that a plastic procedure like that used in Heller's operation for cardiospasm or in the Fredet-Rammstedt operation for pyloric stenosis could be tried, and such a procedure was actually carried out. After this his general condition improved, and for the first time in his life the patient had a spontaneous bowel movement. After three months, however, there was a recurrence, and a few months later he had to be hospitalized for an obstruction. The patient was now 19, but still looked as poorly nourished and infantile as before. A total colectomy was now carried out. In the two years that have elapsed since this operation the patient has been physically and mentally transformed. He has a healthy, agile, mind and body. The authors feel that the remarkable results that followed total colectomy support the theory of toxic absorption, for some factor must have entered the system from the colon to retard growth and development. In recent years interest has been focused also on growth-promoting factors such as vitamin B_{12}. Perhaps in megacolon the absorption of these substances is prevented by the effects of stagnation in the dilated large bowel, effects which may even retard endocrine function.

Medical Journal of Australia, Sydney

2:145-180 (Aug. 2) 1952

Standard of Weight for Height and Age of Australian Women. J. M. Woodhill.—p. 145.
Function of Chest Clinic. A. King.—p. 151.
Tuberculosis Case Finding in Perth. F. E. Heymanson.—p. 153.
Report on Pulmonary Tuberculosis in General Hospital. R. Anderson.—p. 154.
Outbreak of Bornholm Disease in New Guinea. C. E. M. Gunther.—p. 157.
Cutaneous Inoculation Tuberculosis with Report of Case. F. S. Owen.—p. 158.

2:181-212 (Aug. 9) 1952. **Partial Index**

Simplified Table of Food Composition for Use in Evaluation of Australian Diets. J. M. Woodhill.—p. 188.
Diets of Group of Pregnant Women Living in Sydney. J. M. Woodhill.—p. 192.

Minerva Chirurgica, Turin

7:449-506 (June 30) 1952. **Partial Index**

*Denervation of Carotid Sinus in Essential Epilepsy. T. Bandini.—p. 449.
Benign Tumors of Stomach: Synthetic Review and Contribution of Surgical Department of City Hospital of Turin from 1938. M. Ferrando and C. Brunetti.—p. 452.
Pathogenesis and Rational Therapy in Surgery (Pathogenetic Bases for Rational Therapy of Intestinal Obstruction). A. Bobbio.—p. 467.

Denervation of Carotid Sinus in Epilepsy.—Denervation of the carotid sinus is indicated in epileptic patients for its effect on the cerebral circulation and the parathyroid glands and for the elimination of reflexogenic centers. It is contraindicated in young patients because of the action of the carotid sinus on growth and in older patients who have arteriosclerosis. Although with anesthesia of the intercarotid area the operation is easy and well tolerated, it should be performed only after all medical therapies have failed, and when clinical, radiological, and ventriculographic investigations have not revealed the presence of organic focal lesions. The author reports late results in 12 of 32 epileptic patients in whom he performed bilateral denervation of the carotid sinus. A 34-year-old man who had seizures every week or every other week preoperatively has been well since the operation was done in 1937. A 43-year-old woman who had seizures daily preoperatively recovered completely following operation in 1938. There was an improvement in four patients, and in six the condition remained unchanged.

Münchener medizinische Wochenschrift, Munich

94:1642-1695 (Aug. 15) 1952. **Partial Index**

*Tumor Diagnosis with Quinacrine (Atabrine). H. Cramer and C. Brilmayer.—p. 1642.
Results of Splenectomy in Constitutional Hemolytic Anemia (Without Jaundice). M. Donner.—p. 1646.
Hematuria in Acute Diseases of Abdomen. F. O. Mayer.—p. 1651.
The Problem of Actinomycosis. L. Wolff and W. Teusch.—p. 1654.

Tumor Diagnosis with Quinacrine (Atabrine®).—It has been demonstrated by several investigators that quinacrine and a number of other acridine compounds inhibit tumor growth in mice. Cramer and Brilmayer reasoned that, if selective storage takes place in the tumor tissue, urinary excretion should be altered. Only a certain percentage of the quinacrine administered orally or by intravenous injection is excreted in the feces and urine in its original form, while about 60% of the drug is stored in the body (particularly in the reticuloendothelial system) and is probably decomposed. Excretion in the urine is ascertained by means of a photospectroscope. The absorption bands occur at wavelengths of 420, 430, and 450 mμ. When the urine of a healthy subject is examined following the injection of 0.1 gm. of quinacrine, the presence of the drug can be proved with the photospectroscope for as long as 8 to 40 hours, whereas in patients with tumors the quinacrine absorption bands are either completely absent or are present for only from one to three hours. In some cases of severe jaundice the excretion of large amounts of bilirubin may cover up the quinacrine bands so that they cannot be seen. Serial tests in over 300 cases revealed that this simple quantitative method fails in only about 15% of the cases. The authors together with Mack devised a more exact quantitative method, which they describe. In qualitative tests, tumor patients showed the quinacrine bands at the most for three

hours, whereas in quantitative tests the excretion period was not shortened. They discuss the causes of the discrepancies between qualitative and quantitative measurements. The question of extinction or veiling of the typical quinacrine bands during qualitative measurements is discussed and investigated by means of tests. It was found that the reaction occurs only in man and not in the laboratory. The authors also attempted to measure qualitatively several dyes other than quinacrine.

Nordisk Medicin, Stockholm

48:1085-1116 (Aug. 8) 1952. **Partial Index**

Endobronchial Intubation. E. Carlens.—p. 1090.
Local Sequels After Endotracheal Intubation. S. Jørgensen and C. Thorshauge.—p. 1093.
*Laryngeal Complications After Protracted Endotracheal Intubation in Patients with Narcotic Poisoning. W. Dam and E. Zwergius.—p. 1095.

Laryngeal Complications After Endotracheal Intubation.—Following intubation of 143 patients with narcotic poisoning in the psychiatric department of Bispebjerg Hospital 16 slight transient laryngeal complications occurred, 7 serious complications, and 10 obstructing complications. In four of the last group both subjective and objective symptoms soon disappeared, four patients still have symptoms in spite of long-continued treatment, one patient died five days after admission from the poisoning, and one died 11 months later from laryngeal complications. On the basis of their experience Dam and Zwergius suggest the following precautions for the reduction of laryngeal complications following intubation of patients with narcotic poisoning: Intubation should be of as brief duration as possible; soft and relatively small caliber Magill tubes should be used, not exceeding no. 10 for men, no. 8 for women; the tubes should be sterile and oiled before use with sterile petrolatum (vaseline®) and intubation itself must be carried out as gently as possible. They caution against blind intubation and use of a mandrin. The indications for tracheotomy are difficult to establish. Patients can apparently be intubated for 24 hours without danger of complications; after this time the patients must be closely observed on changing the tubes. In case of stridor and reactive changes in the larynx, tracheotomy is advised. This rule may lead to operation in too many patients, but one too many is better than one too few. Treatment by rule of thumb carries with it no permanent drawbacks, whereas too protracted intubation may result in the gravest consequences. Intubation for more than four days is not advocated.

Presse Médicale, Paris

60:1175-1190 (Sept. 6) 1952

Kidney and Functional Adaption to an Overload of Urea and Sodium Chloride. L. Binet and P. Dejours.—p. 1175.
*Spontaneous Intracerebral Hematoma; Study of 18 Cases. C. Gros and J. Minvielle.—p. 1176.
*Procedure for Biological Diagnosis by Demonstrating the Virus in Meningeal Forms of Poliomyelitis. L.-A. Martin, J. Delon, J. Grévin and others.—p. 1179.

Spontaneous Intracerebral Hematoma.—The occurrence of spontaneous intracerebral hematoma is reported in 14 men and 4 women between the ages of 22 and 60, the average age being 44 years. In younger adults this complication has a sudden onset; it is manifested by severe headache followed by focal symptoms and a temporarily clouded state of mind. Subacute and even chronic forms with successive recurrences may be observed. At a later stage the intracranial hypertension increases, but diagnosis of the hematoma should have been considered before this period. In this series electroencephalograms revealed definite focal signs in nine patients. Cerebral arteriography showed displacement of the anterior cerebral artery and of the sylvian artery by the hematoma, but new vessels similar to those associated with multiform glioblastoma and aneurysmal or angiomatous malformations were not observed. The arteriogram thus showed the characteristics of an avascular tumor. During ventriculography, by which the diagnosis may be established, the trocar penetrated the hematoma in three cases, while in two others the fluid of only one ventricle was xanthochromic, and the hematoma was seen to communicate with a lateral ventricle. Clinical localization of the hematoma is nearly always possible, particularly if the hematoma occurs in the temporal lobe, which is the commonest location, or in the ventricular bifurcation: homonymous lateral hemianopsia was highly significant in five of these cases. Patients with spontaneous intracerebral hematoma should be subjected to neurosurgical examination. Exploration should be carried out with a wide osteoplastic flap. Recovery with minimal sequelae will be obtained by thorough evacuation of the hematoma. Differential diagnosis of spontaneous intracerebral hematoma from encephalomalacia and large cerebral hemorrhage, which require different methods of treatment, may be based on the evolution of symptoms and on the vegetative and electroencephalographic signs.

Biological Diagnosis of Meningeal Forms of Poliomyelitis.—The occurrence of a meningeal syndrome with headache, vomiting, constipation, and restlessness is reported in five children between the ages of 8 and 13 and in three adults between the ages of 25 and 47. Three patients had severe myalgia, three others had photophobia, and two of the latter had vertigo. Kernig's sign was positive in all patients, and all had stiffness in the neck. The reflexes were normal in two, diminished in two, exaggerated in one, abolished in two, and varied in one. The syndrome persisted for four to eight days. The patients were emaciated and recovery was slow. Diagnosis of virus meningitis was based on the clinical aspect, while the poliomyelitic nature of the pathogenic agent was established by repeated tests on rabbits, including serial passages, crossed immunity, and neutralization of the virus after in vitro mixture with an antipoliomyelitic serum. The sensitivity of the rabbit to the virus of poliomyelitis, established by Blanc and Martin in 1948, thus made it possible to demonstrate the virus in the feces and blood of the authors' patients with nonparalytic poliomyelitis of meningeal type.

Revista Médica de Chile, Santiago

80:259-322 (May) 1952. **Partial Index**

Hemostasis in Patients with Hepatobiliary Disease. H. Alessandri, H. Ducci and R. Katz.—p. 259.
*Treatment of Herpes Zoster with ACTH and Cortisone. M. Weinstein and R. Lamas.—p. 266.
Anorectal Fistula and Cancer. A. Schwartz and R. Marin V.—p. 284.
*Purpura Necrotica. C. Larrain, O. Munita, I. Montes and N. Sainz. —p. 291.

Treatment of Herpes Zoster with Corticotropin and Cortisone.—Corticotropin (ACTH) and cortisone produced prompt relief of pain and early regression of the eruption in nine patients with herpes zoster and three with postherpetic neuralgia. These patients were between 10 and 73 years of age. Cortisone was given in tablet form at the rate of 12.5 mg. every six to eight hours for from two and one-half to six days. Corticotropin was given intravenously in doses averaging 1 mg. daily, each infusion (1,000 cc.) taking eight hours; in most cases four infusions were needed. The medications were tolerated without side-effects, in spite of the fact that several of the patients were aged and one had hypertension. Relief of pain generally began within one-half hour after treatment was started; regression of the eruption took longer, but could be observed within 24 hours, with diminution of erythema and softening of the blisters, which dried up rapidly in the succeeding days. There were no neuralgic sequelae when treatment was begun early in herpes zoster. One patient with neuralgia of 54 days' duration was improved but not entirely free from pain when discharged from the hospital; the other two with postherpetic neuralgia were cured. Corticotropin given intravenously seemed to act more rapidly and effectively than cortisone, but both remedies proved superior to other medications customarily used in treating herpes zoster.

Purpura Necrotica.—Ingestion of cinchophen coincided with the onset of a fatal attack of purpura necrotica in a woman of 45. The history showed that she had had repeated attacks of nosebleed up to the age of 12, when they ceased spontaneously. Subsequently she had profuse menstruations lasting 10 and even 15 days. No other hemorrhages were recorded. Her illness began with polyarticular pain; after the first day she took 6 tablets of cinchophen (atophan®) (0.5 gm. each), 1 gm. every hour, for relief of pain. With the sixth tablet, rapidly confluent purpuric

patches appeared on her chest, face, abdomen, and limbs. These lesions were quickly transformed into enormous ecchymoses. The patient was admitted to a hospital the following day. Examination showed ecchymoses involving the entire back, the forehead and part of the scalp, and the area around the mouth. The spleen was not enlarged; the liver, slightly painful and firm, was palpable below the costal margin; tachycardia was present, but the temperature did not exceed 37.5 C during the first fortnight. The patient's general condition was poor, and she ate with difficulty. She was given 2,400,000 units of penicillin and 1.5 gm. of streptomycin daily to prevent or combat secondary infection. Other measures, including blood transfusions (1,400 cc. of stabilized blood in all), amino acids, vitamin therapy, and glucose, were tried but without success. The lesions became necrotic, dry gangrene developed, and the temperature increased, fluctuating between 38 and 39 C during the two weeks preceding death, which occurred one month after the first appearance of the disease. Blood studies had shown a steadily increasing anemia and thrombocytopenia, and the findings at autopsy included cloudy swelling and discrete lipoidosis of the liver in addition to the necrotic lesions. Skin tests for cinchophen sensitivity were not made; consequently, a causal relationship between the patient's illness and the cinchophen tablets she took cannot be established.

Rivista di Clinica Pediatrica, Florence

50:432-508 (July) 1952. **Partial Index**

Changes Caused by Cortisone on Tuberculin Reaction. R. Rossi and G. Bartolozzi.—p. 433.
*Differential Findings in Evolution of Experimental Tuberculosis in Guinea Pigs Treated with Cortisone, Streptomycin, and Cortisone Combined with Streptomycin. F. Ragazzini.—p. 451.
Idiopathic Cardiac Hypertrophy. D. P. R. Keizer.—p. 470.

Cortisone in Experimental Tuberculosis. — Experiments were made in 45 guinea pigs inoculated with Myco. tuberculosis to test the hypothesis that cortisone inhibits the formation of granuloma and thus facilitates the action of streptomycin. Cortisone alone in daily doses of 2 mg. was given to 15 animals. Of these five received the hormone beginning on the day of inoculation, five received it one week after inoculation, and five received it three weeks after inoculation. Streptomycin in daily doses of 5 mg. was given to five animals one week after inoculation and to five animals three weeks after inoculation. A daily dose of 2 mg. of cortisone combined with 5 mg. of streptomycin was given to five guinea pigs one week after inoculation and to five animals three weeks after inoculation. Of the 10 animals that served as controls five were killed 52 and five 68 days after the inoculation. Cortisone alone did not change greatly the tuberculous picture, although there was milder necrosis and a greater proliferation of epithelioid cells in these animals than in the controls. Results were better in the animals treated with cortisone combined with streptomycin than in those treated with streptomycin alone. The groups of histoid and epithelioid cells did not have a tendency to unite in micronodular formations as happened in those that received only the antibiotic. This fact, the good general condition of this group of animals at the end of the treatment, and the findings at autopsy confirm the inhibiting action of the hormone, which did influence the action of the antibiotic. Since the differential findings were more evident in the group in which treatment was begun one week after the inoculation, it is suggested that the therapy instituted when a condition of hyperergy was already present may have attenuated with its antiallergic action the dangerous effects of hypersensitiveness without impairing the secondary onset of immunity and thus helping indirectly the action of the antibiotic.

Tubercle, London

33:257-286 (Sept.) 1952

Actinomycosis of Lung. Actiology, Diagnosis and Chemotherapy. L. P. Garrod.—p. 258.
Collecting Clinical Data in Chest Clinic. P. Stradling.—p. 266.
Congenital Tuberculosis. W. C. Harris and H. J. Trenchard.—p. 273.
Development of Drug Resistance to Isoniazid in Cases of Pulmonary Tuberculosis. D. A. L. Bowen and D. M. Collins.—p. 276.
Transient Atelectasis of Healthy Lobe Associated with Artificial Pneumothorax. A. C. Penman and J. S. Miller.—p. 278.

Ugeskrift for Laeger, Copenhagen

114:993-1026 (July 24) 1952. **Partial Index**

*Aspiration of Amniotic Fluid in Newborn. W. Munck.—p. 998.
Congenital Stridor with Special Regard to Hyperplasia of Thymus. H. J. Lauritzen.—p. 1003.
Two Cases of Primary Carcinoma of Appendix. E. Ingemann Jensen. —p. 1012.
Acute Malignant Lymphogranulomatosis (Hodgkin's Disease). Three Atypical Cases with Fever and Slight Anemia as Only Symptoms. M. Osler. —p. 1016.

Aspiration of Amniotic Fluid in Newborn.—Intrauterine aspiration of amniotic fluid probably occurs in all fetuses immediately before and during delivery, especially in cases of intrauterine asphyxia. In the course of a few hours membranes, which are believed to come from the vernix and are called vernix membranes, may be formed along the alveolar walls. The aspiration is often accompanied by extensive atelectasis of the lung tissue and gaseous exchange in the lungs becomes extremely difficult. The aspiration can lead to the development of pneumonia. The condition is dangerous, particularly for premature infants, and is often the cause of death in the first days of life. Fifteen cases of death within the first four days of life are reported. Amniotic fluid aspiration was the sole cause of death in 4 of the 12 premature infants and in one of the 3 fullterm infants and was the contributing cause of death in the remaining cases. Munck recommends energetic active treatment, and also stresses the importance of careful and expert treatment of all premature infants in the first days of life.

Wiener medizinische Wochenschrift, Vienna

102:605-648 (Aug. 16) 1952. **Partial Index**

Experiences with Subarachnoid Injections of Alcohol. L. Beichl.—p. 607.
Rhesus-Immunization by Intramuscular Injections of Heterogeneous Blood. H. Bergmann.—p. 609.
*Pneumonectomy in Childhood. W. Denk.—p. 610.
Exclusion Gastrectomy in Cases of Duodenal Ulcer in Which Excision of the Ulcer is not Feasible. H. Finsterer.—p. 612.
Modern Antibiotics. F. Gilligsberger, W. Kerschner and J. Monauni. —p. 619.

Pneumonectomy in Childhood.—Of 29 children between the ages of 3 and 16 years with various diseases of the lungs, 4 were subjected to segmental resection, 17 to lobectomy, 3 to lobectomy and segmental resection, and 5 to pneumonectomy. Thirteen children were operated on for bronchiectasis, five for congenital cystic disease of the lung, four for chronic abscess-forming "foam cell" pneumonia of Chiari, two for tuberculosis refractory to conservative treatment, two for congenital bronchial cysts, one for bronchial adenoma, one for a benign tumor of the right upper lobe, and one for an aspirated spruce twig. One 14-year-old child died of cardiac decompensation on the second day after pneumonectomy, which was performed as a last resort to save the life of the patient who had chronic suppurative pneumonia, extensive bronchiectasis and hemorrhage from the pulmonary artery due to erosion. Of the remaining 28 children, 24 made a complete recovery and 4 were improved. Lobectomy or segmental resection is particularly indicated in children with bronchiectasis; of the 13 children operated on for this condition 10 were cured and 3 were improved, the postoperative follow-up varying from two months to three and a half years. Of the five children with congenital cystic disease of the lung, the indication next in order of frequency, four made a complete recovery and one had still a small residual cavity. It is noteworthy that three of these children who were subjected to excision of the entire right or left lung could run and jump after the operation like normal children. The patients with tuberculosis, bronchial cysts, lung tumors, and the one who nine months before the surgical intervention had aspirated a spruce twig 3 cm. in length recovered completely. The postoperative follow-up varied from two and a half months to four years. The satisfactory results obtained by the author's patients who did not show any signs of respiratory insufficiency at rest or when running or jumping warrant a favorable prognosis without reduced functional capacity in children who have been subjected to lobectomy or pneumonectomy.

BOOK REVIEWS

Cardiography in General Practice: Electrocardiography, Vectorcardiography and Ballistocardiography. By Abraham I. Schaffer, M.D., Assistant Visiting Physician, Metropolitan City Hospital, New York. Cloth. $3. Pp. 135, with 55 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1952.

This small volume is intended to serve as a brief introduction to clinical electrocardiography for the general practitioner or clinician. The newer methods of vectorcardiography and ballistocardiography are also discussed briefly. Special emphasis is placed on how the electrocardiographic tracing is produced and its significance. The book is clearly and accurately written and effectively illustrated. Although it is not a comprehensive work on electrocardiography, it is recommended to those who wish to acquire a working knowledge of this science. To such persons it will provide a theoretical foundation for clinical interpretation to which, later, more detailed study can be added.

The 1951 Year Book of Endocrinology (January, 1951-January, 1952). Edited by Gilbert S. Gordan, M.D., Ph.D., Assistant Professor of Medicine, University of California School of Medicine, San Francisco. Cloth. $5. Pp. 415, with illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1952.

This book presents a review of endocrinology reports published during 1951. Sections are devoted to the pituitary gland, the thyroid gland and exophthalmos, the parathyroids, calcium metabolism and metabolic bone diseases, the adrenal medulla, the adrenal cortex, cortisone, corticotropin and allied compounds, sexual precocity, female reproductive system, the testes, diabetes mellitus and carbohydrate metabolism, and endocrine treatment of neoplastic diseases. Editorial comments introduce each section and supplement a number of the abstracts. Clinical reports predominate, but a number of experimental studies are included. This volume can be recommended to the busy practitioner wishing to keep in touch with the latest developments in the field of endocrinology.

The 1951 Year Book of Drug Therapy (September, 1950-August, 1951). Edited by Harry Beckman, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee. Cloth. $5. Pp. 502, with 91 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1951.

This book contains abstracts of selected articles pertaining to drug therapy published between September, 1950, and August, 1951. The abstracts, largely culled from domestic journals, cover the fields of allergy, cardiovascular diseases, dermatology, endocrinology, gastroenterology, hematology, internal medicine, neuropsychiatry, obstetrics and gynecology, ophthalmology, otorhinolaryngology, pediatrics, roentgenology, surgical specialties, and venereal diseases. Editorial comments follow many of the abstracts, drawing attention to related studies, pointing up the significance of a report, or adding a note of conservatism. This book can be recommended to the busy practitioner as a means of keeping abreast of recent developments in clinical pharmacology.

A Textbook on the Nursing and Diseases of Sick Children for Nurses by Various Authors. Edited by Alan Moncrieff, M.D., F.R.C.P., Nuffield Professor of Child Health, University of London, London. Fifth edition. Cloth. 37s. 6d. Pp. 770, with illustrations. H. K. Lewis & Co., Ltd., 136 Gower St., London, W.C.1, 1952.

This book is designed to provide a textbook for the nurse entering the final state examination. It conforms to the syllabus for the examination for the certificate for Sick Children's Nurses, issued by the General Nursing Council for England and Wales. The material exceeds these strict requirements, since it was designed to be as complete as possible, serving both as a work of reference and as a standard textbook. The book is divided into two parts, containing 36 chapters and 161 photographs and illustrations. Part 1 deals with general nursing procedures and considerations in pediatrics. This includes principles of surgical technique. Part 2 is introduced by chapters on diseases and nutrition of the newborn. The following chapters discuss diseases commonest in children, with much attention to orthopedic conditions, their prevention and treatment. The last chapter concerns the care of children in the tropics. The appendix includes material on medicine and pharmacology and brief discussions of speech therapy, physical therapy, roentgenograms, and social work in pediatrics. Also included is a list of questions of a final state examination for the supplementary part of the Register for Sick Children's Nurses.

This book has the advantage of having a number of contributors, each a specialist in a particular subject. It is edited by a physician with wide experience in pediatrics. It represents English thinking, methods, and experience and would undoubtedly meet the needs of nurses in that country; however, the material does not parallel in all respects that which is required of nurses in the United States. For this reason, its value here will probably be limited to that of a reference text.

Fundamentals of Neurology. By Ernest Gardner, M.D., Professor of Anatomy, Wayne University College of Medicine, Detroit. Second edition. Cloth. $4.75. Pp. 359, with 142 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C.2, 1952.

This text is written primarily for students in special fields of science, as well as for nurses, physical therapists, and occupational therapists. It is not intended as a text for medical students or physicians. The author attempts to present the subject as a series of basic concepts that can be used as a foundation for a more detailed study of specific phases of neurology. Revisions and additions have been made to include the new developments in neuroanatomy and neurophysiology. The gross and microscopic structures of various parts of the nervous system are briefly described, and the important facts in regard to the physiology are adequately covered. The effects of lesions in various parts of the neuraxis are briefly discussed. The book is well printed and is easily read. There are a large number of pertinent illustrations that are well reproduced. The few references are given mainly to stimulate students to further reading. There is a fairly long glossary of new terms and an adequate index. The author undertook a difficult task when he attempted to explain the complexities of neuroanatomy and neurophysiology in terms that can be understood by students who have not had a thorough grounding in general anatomy and physiology, but he has been successful in his attempt.

Textbook of Medicine by Various Authors. Edited by Sir John Conybeare, K.B.E., M.C., D.M., Physician to Guy's Hospital, London, and W. N. Mann, M.D., F.R.C.P., Assistant Physician to Guy's Hospital. Tenth edition. Cloth. $8. Pp. 912, with 31 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1952.

In the preface to this textbook by 17 British authors, the senior editor, Sir John Conybeare, states that its aim is still to provide, within as small a compass and at as low a price as possible, the essentials of medicine. The total length of the volume has been kept below 1,000 pages, in spite of the fact that it discusses not only the topics usually included in American textbooks of medicine but also such subjects as diseases of infants, common diseases of the skin, examinations for life insurance, and the sulfonamides and antibiotics. As a result, some of the chapters are briefer and less comprehensive than those found in many American works. In addition to the text, this volume contains tables of normal laboratory values, normal height and weight for adult males, metric and apothecaries' equivalents, and relative effectiveness of antibiotics in various infections. With this edition there have been several changes in contributors, and Dr. W. N. Mann has become co-editor. Many sections, especially those on therapy, have been rewritten to bring

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The reviews here published have been prepared by competent authorities and do not represent the opinions of any official bodies unless specifically stated.

them up-to-date. The format of the book is attractive, and the type is large and clear. There are 31 roentgenograms of good quality but few clinical illustrations. The index appears adequate. This should prove a useful text for students.

The Knee and Related Structures: Injuries—Deformities—Diseases—Disabilities. By Philip Lewin, M.D., F.A.C.S., F.I.C.S., Professor and Chairman of Department of Bone and Joint Surgery, Northwestern University Medical School, Chicago. Cloth. $16. Pp. 914, with 335 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1952.

The avowed purpose of this book is to boil down the immense and confusing material that has appeared in articles on the subject of the knee joint. In this attempt the author has succeeded splendidly, not only by the wealth of his collected material but especially by the unique manner in which the material is presented, step by step, from the anatomy, physiology, and biomechanics to the clinical interpretation. This he has done with his usual didactic force and by his pursuit of a path of logic in drawing therapeutic conclusions. If the manner of presentation may be unique, it has its propaedeutic advantages.

A condensed view of the many aspects of the approach to the diagnosis and care of knee disorders is unfolded by the author in somewhat epigrammatic form in the introduction, before the problem is continued more systematically in the following chapters. The chapter on the anatomy of the knee is remarkable for its detail and painstaking presentation. The next, on biomechanics, is more succinctly treated, although most pertinent facts are mentioned, which is also the case in the following chapter on etiology. The chapter on physical education, though rather concise, is remarkably complete and instructive. We find also that the chapter on roentgenology is more explicit, with special consideration being given to x-ray technique. The chapter on laboratory procedures contains sufficient detail for general orthopedics, but the one on differential diagnosis is especially interesting, since it reveals a good diagnostic acumen and is highly discriminatory in its interpretation. It is one of the best and is of special importance to the clinician. There are chapters on prognosis that have the usual difficulties of presentation; but the author makes some illuminating points concerning the appraisal of litigious and contentious patients. He then gives a discussion on conservative treatment that contains many shrewd observations and sound practical hints. It is fortunate, in his discussion of the surgery, that he has not omitted preoperative preparation such as choice of anesthesia and that he gives special attention to postoperative care.

The field of so-called internal derangements of the knee joint naturally occupies a very large portion of the book. The author gives special consideration to the mechanogenesis of the meniscus lesions, discussing a great variety of these, and he does not omit the vexing question of meniscus regeneration. A good deal of space and special care is devoted to the operative technique for all types of internal derangement. Everything is discussed, from an impinged fat pad to a fracture of the tibial spine or the rupture of the gluteus. The section on external derangement of the knee includes such conditions as the rupture of the patellar ligament or anomalies or disorders of the patella. This is followed by a chapter on the flexion contractures of the knee and one on deformities, arthritic or congenital. All deformities are well represented and distinctly illustrated.

There is a chapter on industrial injuries to the knee that is of interest, as is the chapter on fractures in and around the knee joint. The chapters on fractures, dislocations, osteomyelitis, and tuberculosis enjoy a very detailed presentation and reach considerably beyond the conventional bounds. The author gives special attention to arthritis, emphasizing the conservative methods that are now so often ignored or scorned. Spastic and infantile paralysis are well considered, but one of the most interesting chapters is that on tumors, which are treated with special care. This is followed by chapters on length equalization and by an appendix in which such topics as embryology, surgical approaches, and psychological aspects are discussed in somewhat unconventional sequence.

Because of the astounding wealth of information and the great abundance of detail the book is not easy reading, but it is an unusually complete source of information on the subject, and it is a great credit to the author's assiduity, experience, and didactic skill of presentation.

The Diagnosis of Nervous Diseases. By the late James Purves-Stewart, K.C.M.G., C.B., M.D., Consulting Physician to Westminster Hospital, London, and C. Worster-Drought, M.A., M.D., F.R.C.P., Physician to West End Hospital for Nervous Diseases, London. Tenth edition. Cloth. $10. Pp. 962, with 388 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1952.

This revision of the work was almost entirely completed before the death of the senior author in 1950. The 10th edition follows closely the pattern of previous editions. Some chapters have been rewritten, and the material in all the chapters has been brought up-to-date. The format of the book is good. The type is clear and easily read. There are a large number of pertinent illustrations, well reproduced, and an adequate index.

Disorders of the nervous system are considered from an anatomic-physiological viewpoint, without any extensive discussion of clinical entities. The major portion of the book is concerned with a discussion on the anatomic and physiological basis of symptoms, such as coma, convulsive phenomena, aphasia, paralyses, and involuntary movements, together with a brief consideration of various disease entities in which these symptoms are a prominent feature. In addition, there are chapters on physiological anatomy, methods of history taking, the psychoneuroses and psychoses, electrodiagnosis, the cerebrospinal fluid, and a long chapter on intracranial tumor. The method of presentation used by the authors is valuable for students, because it clearly elucidates the anatomic and physiological basis of clinical symptomatology. The practitioner, however, will not find a comprehensive description of clinical syndromes or advice regarding therapy.

Hormones: A Survey of Their Properties and Uses. Published by direction of Council of Pharmaceutical Society of Great Britain. Cloth. 35s. Pp. 220, with 34 illustrations. Pharmaceutical Press, 17 Bloomsbury Sq., London, W.C.1, 1951.

This book presents the history, physiology, chemistry, standards, actions, uses, and the pharmacy of the hormones. It also presents details of the commercial preparations of endocrine substances now in common use. Although prepared to satisfy the needs of pharmacists, it contains much that would be of interest to the practicing physician. The chapters on history, physiology, and chemistry of the nonsteroid and steroid hormones are examples. The chapter on standardization contains an extensive bibliography that would be valuable to laboratory workers. The section on actions and uses is somewhat sketchy but probably is sufficient for pharmacists. The section on pharmacy describes methods and formulas for a variety of preparations including injections, solutions, ointments, creams, and suppositories, approved methods of sterilization, conditions for storage, and requirements of the Therapeutic Substances Act of Great Britain. The last chapter will be of little interest to readers in the United States and elsewhere outside the British Empire, since the manufacturers listed in this chapter are British and no manufacturers of similar products elsewhere in the world are listed. All in all this is a valuable little text, which, while not complete or too detailed, nevertheless presents sufficient information to make it useful to general practitioners and students as an epitome of the subject.

Metabolic Interrelations: Transactions of the Third Conference, New York, N. Y., January 8-9, 1951. Edited by Edward C. Reifenstein, Jr., M.D., Oklahoma Medical Research Institute and Hospital, Oklahoma City, Oklahoma. Editorial Assistant: Clydelle Brownfield. Cloth. $4. Pp. 294, with 85 illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

This publication consists of 15 reports on current researches related to the biochemistry and histology of bone formation and bone resorption. Topics discussed include osteogenetic potency and osteogenetic inductor substances, the nature of bone and phosphate rock, the role of phosphatase, the effects of pituitary factors and of thyroxin on skeletal morphogenesis in the rat, and the electron micrography of bone. Each report is presented by a prominent worker in the field and is followed by a lively discussion by other participants of the conference. The volume should be of interest to those wishing to familiarize themselves with recent developments in the field of bone metabolism.

QUERIES AND MINOR NOTES

DRUGS AND WEIGHT REDUCTION

To the Editor:—*I know more than 25 overweight patients who have been treated by another physician and who have consistently lost weight while taking certain unknown (to me) medication that he has prescribed. No untoward effects have occurred in any of them. This doctor imposed no diet restrictions whatever. What medicaments can cause constant loss of weight and yet produce no untoward symptoms?*

M.D., New York.

Answer.—There is no known drug capable of reducing body weight without any likelihood of producing undesirable side-effects. Amphetamine and methamphetamine have a depressant effect on the appetite; however, persons receiving these drugs often complain of restlessness, palpitations, and insomnia. These agents should be used only as adjuncts to a suitable dietary regimen in selected cases of obesity. At one time dinitrophenol was employed to effect weight reduction. This drug could produce a tremendous acceleration in the metabolic rate but also was responsible for the development of skin rashes, cataracts, agranulocytosis, and fatal hyperpyrexia. Accordingly, dinitrophenol has fallen into disrepute, inasmuch as its potential usefulness is clearly outweighed by toxic hazards. Thyroid extract is also capable of producing serious side-effects and should not be employed in the treatment of obesity, unless hypothyroidism is present. There are many products, including mixtures of vitamins and minerals, that are being promoted for effecting weight reduction. Any value they may have is probably manifest as a psychological aid or reminder to the patient that he must reduce his caloric intake.

OBESITY IN 29-YEAR-OLD WOMAN

To the Editor:—*A 29-year-old woman weighs 223 lb. (101.1 kg.) and has a blood pressure of 160/100 mm. Hg. She has moderate hirsutism of the face, chin, chest, back, arms, and legs, with a slightly male pubic hair distribution. Her hair was somewhat thin on the top of her head, and she has been losing some hair. Her basal metabolic rate is +5, her urine and glucose tolerance are normal. After eight months of conscientious dieting, assisted by use of* d*-amphetamine sulfate (dexedrine®), 10 mg. three times a day, during which she listed the food eaten, her weight was down only to 204 lb. (92.5 kg.). Roentgenograms of the skull, spine, and femurs were normal. I sent her to an endocrinologist, who had a 17-ketosteroid estimation done, the result of which was 15.6 mg. per 24 hours. This was considered a high normal for her age group. The endocrinologist has recommended a bilateral wedge-shaped resection of the ovaries. The patient is well-balanced emotionally and was planning to be married.*

Edward G. Bourns, M.D., Westfield, N. J.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—The inquiry makes no mention of whether this patient is menstruating normally. If amenorrhea is included among her symptoms and if she has large, polycystic ovaries, she would seem to have the so-called Stein-Leventhal syndrome (Stein, I. F., and Leventhal, M. L.: *Am. J. Obst. & Gynec.* **29**:181 [Feb.] 1935), for which bilateral wedge resection of the ovaries has been recommended for reestablishment of menstrual function and cure of the commonly associated sterility. Good results have been reported for this procedure not only by the original authors but by a number of others. These good results, however, pertain to the amenorrhea and sterility, and there would seem to be no rationale in resorting to such a procedure if menstruation is normal and sterility is not a part of the patient's problem.

Answer.—The main features of this brief outline are obesity, hirsutism, hypertension, and a slight increase in the excretion of 17-ketosteroids. It is unfortunate that no record is given of the patient's menstrual history. It is most important to determine whether the patient is producing an excess of androgen. One of the simplest ways of doing this is to make further determinations of the 17-ketosteroid excretion. If it is somewhat elevated, exploration of the ovaries and adrenals might be justified. It is difficult to see how a bilateral wedge-shaped resection of the ovaries would improve her condition; in fact, the ovaries should not be touched unless they contain some androgen producing tissue. No attention can be paid to the patient's statement that she has failed to lose weight despite her adherence to a weight reducing diet, even though she has kept a record of what she has eaten. It is important to determine whether the hirsutism is related to an ovarian deficiency producing a relative excess of androgen or a masculinizing tumor producing an absolute excess of androgen.

PUBIC HAIR ON YOUNG GIRL

To the Editor:—*What significance should be attached to finding long, black, curly pubic hairs over the lower portion of the vulva in a 6-year-old girl? She has no evidence of hypertrichosis, and there are no other secondary sex characteristics present. She is hyperactive and is 5 lb. (2.3 kg.) under the average weight for her height and age; she has a mild deficiency anemia but is otherwise normal on examination.*

M.D., Pennsylvania.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—It may be that the youngster has a nevus involving the hairs in the area, and, if so, it is of no significance. The hairs should be examined microscopically for evidence of abnormalities either in their structure or from infection.

Answer.—The finding of long, black, curly pubic hair over the lower portion of the vulva in a 6-year-old girl may or may not be of definite significance. Sometimes a few pubic hairs appear long before the onset of puberty. The size of the clitoris should be carefully checked and the excretion of 17-ketosteroids in the urine determined. If the excretion is within normal limits, the clitoris is not enlarged, and no other secondary sex characteristics are present, treatment at present would seem unnecessary, but the patient should be examined about every six months.

EXCESSIVE PERSPIRATION OF FEET

To the Editor:—*I see many children who have excessive perspiration of the feet, which causes the feet to become white and scalded in appearance. Is there anything that can be done to prevent this condition?*

Frank A. Andrews, M.D., Coldwater, Mich.

Answer.—Excessive perspiration of the feet in children is usually due to a vasomotor action. Local sweating usually occurs in the parts of the body in which the sweat glands are most highly developed. These areas are the scalp, face, axillas, palms, and soles. Occasionally, pressure on the plantar nerve resulting from flat feet may cause excessive sweating. Correction of a tendency toward flat feet may prevent the excessive sweating that causes the feet of these children to become white and scalded in appearance. The wearing of too heavy socks or shoes may cause excessive perspiration and should be avoided. The use of a soothing talc in the socks and shoes may aid in cutting down the perspiration and avoiding this condition.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any official bodies unless specifically stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

STUNG BY 100 YELLOW JACKETS

To the Editor:—*A man, 37, previously in sound health, was stung by about 100 yellow jackets on Sept. 6, 1949. His body was swollen and seemed blanched almost throughout. He had edema of the face and larynx and had to be given epinephrine, antihistaminics, and opiates for relief. Twenty-four hours later he felt so much better that he drove to his job and, on leaving his automobile, was stricken with what was diagnosed as right sided cerebral thrombosis producing left hemiplegia and difficulty in deglutition and phonation. At present he has mild weakness of the left side, slight difficulty in swallowing, and a noticeable phonation defect. Can the thrombosis have been caused by the stings of the yellow jackets?* *M.D., Georgia.*

Answer.—The stings of 100 yellow jackets in one encounter, even to a man in sound health, is a great hazard and could easily be fatal. The probability is that this person was not definitely sensitive to the sting of the insect, otherwise, his chance of survival would have been remote. No doubt the thrombosis, with resulting hemiplegia, was the direct result of the stings of the yellow jackets. The venom of the bee and probably of the other Hymenoptera, including the yellow jacket, is a complex substance from which various components have been isolated: choline, glycerol, phosphoric acid, palmitic and other fatty acids, and, more important than any of these, a non-nitrogenous constituent suggestive of saponin, which probably constitutes the active principle of the venom. Bee venom reacts exactly the same on a strip of virgin guinea pig uterus as does a suitable concentration of histamine in the bath. It seems fair to conclude that the venom of the bee, and likewise of the yellow jacket, is similar in its action to histamine, which causes dilatation of the capillaries and extravasation of corpuscles and plasma into the surrounding tissue. It seems probable, therefore, that these changes are capable of leading to thrombosis of any thin-walled cerebral vessel, which may become clinically extensive, even to the point of causing paralysis. This man should by all means avoid further encounters with Hymenoptera.

MILD UREMIA

To the Editor:—*A 45-year-old priest has an elevated nonprotein nitrogen level (66 mg. per 100 cc.). His mother died of uremia at the age of 59. My diagnosis is chronic interstitial nephritis. Retrograde pyelograms are normal. The concentration and dilution tests are slightly abnormal. The patient has a persistent tremor of the hands, and his basal metabolic rate is —19. The cephalin-cholesterol flocculation test result was normal, and the blood pressure is normal. In the past two years, the patient has had two attacks of bursitis in the shoulder, and roentgenograms show some arthritic changes. He has taken penicillin and for the past two months has been taking chloramphenicol, in the hope that this might help his kidney disorder. He has no albumin in the urine, however. Despite this treatment, the nonprotein nitrogen level and the sedimentation rate went higher. I would appreciate any suggestions.*

Albert T. Kwedar, M.D., Springfield, Ill.

Answer.—An elevated blood urea level without hypertension, albuminuria, or an abnormal number of red blood cells or pus cells in the urine suggests either obstructive uropathy or adrenal insufficiency. Normal results of cystoscopic examination and retrograde pyelograms rule out obstruction in this case. A careful study of a fresh, acid specimen of urine, taken after 15 hours without fluid intake, should rule out minimal proteinuria, broad casts, and red blood cells, as would be expected in chronic nephritis. There is no indication for using antibiotics in mild uremia unless there are associated pyuria and bacilluria. When results of urine tests are normal, the prerenal causes of a rise in blood urea, and especially adrenal cortical hypofunction (Addison's disease), must be ruled out. If the Thorn test is negative and hypopituitarism or hypoadrenia are disproved by insulin tolerance tests, the patient should be treated with a diet adequate in calories but low in protein. It is unlikely that any symptoms result from metabolite retention until the nonprotein nitrogen or blood urea level is over 150 mg. per 100 cc. and the blood hemoglobin level is below 9 gm. per 100 cc.; however, in adrenal dysfunction weakness occurs with minimal rise in the blood urea level. Patients with adrenal cortical hypofunction usually have normal erythrocyte sedimentation rates unless the disease is due to adrenal tuberculosis.

RECURRENT HERPES SIMPLEX

To the Editor:—*A 35-year-old white woman has had extremely painful recurrent herpes simplex for 30 years. The attacks have occurred every year except one, in May, June, or July, always in the posterior aspect of the left thigh. No precipitating factor has been recognized, and the patient has no other disease or seasonal allergy. Herpes simplex virus was isolated from inoculated adult and unweaned mice, and blood serum taken at five day intervals showed complement fixation titers of 1:32, 1:64, and 1:64, respectively. Neutralizing antibodies were demonstrated in titers higher than those formerly encountered. These tests were carried out by the Viral and Rickettsial Disease Laboratory of the State of California Department of Public Health. The patient has undergone a large number of treatments, including repeated smallpox vaccinations, all without benefit.* *Karl J. Deissler, M.D., Oakland, Calif.*

Answer.—Recurrent herpes simplex, irrespective of its location, is resistant to most forms of treatment. It is seen in association with certain diseases, such as tabes dorsalis, following a bout of lightning pains. Its occurrence in association with the menstrual period is common. Experience with repeated smallpox vaccinations in this disease has shown this to be unsuccessful, and the same may be said for antibiotics. In most patients, the disease runs a self-limited course in which repeated attacks occur at increasingly longer intervals and eventually cease.

THE GOFMAN TEST

To the Editor:—*What is your opinion of the Gofman test for coronary disease?* *M.D., New Jersey.*

Answer.—The so-called Gofman test is not per se a test for coronary disease. Rather, it is an ultracentrifuge analysis, qualitative and quantitative, of the low density β-lipoproteins of serum. This test is based on the work of Gofman and associates on the relationship between specific classes of serum cholesterol-bearing lipoproteins and atherosclerosis (*Science* **111**:166, 1950; *Circulation* **2**:161, 1950; *J. Gerontol.* **6**:105, 1951; *Am. J. Med.* **11**:271, 1951; *Circulation* **5**:119, 1952). They have accumulated evidence indicating that serum levels of lipoproteins having certain flotation rates (S_f 12-20 and S_f 35-100) (data obtained by the test) may be superior indices of "atherosclerogenic potentialities," compared to serum levels of total cholesterol and the total cholesterol to phospholipid ratio. It must be emphasized that the whole problem of the relationship between classes of serum lipoproteins and atherosclerosis is still at the investigative stage. Careful long-term research is required before the prognostic significance and therapeutic implications of lipoproteins in atherosclerosis will be fully clarified. Hence the basis in knowledge does not yet exist for the utilization of this test as an established routine procedure. At present, therefore, the routine submission of serums to laboratories for this expensive test is not indicated.

DIETHYLSTILBESTROL GIVEN DURING PREGNANCY

To the Editor:—*I have noted a high incidence of nevus flammeus and superficial telangiectasia in children born of women given diethylstilbestrol as an antiabortive agent during pregnancy. Has this association been noted by others?*

M.D., New York.

Answer.—No increased incidence of nevus flammeus or superficial telangiectasia has been reported in children born of women given diethylstilbestrol during pregnancy. There is no theoretical reason why the incidence of nevus flammeus should be increased. It has been theorized that large amounts of estrogens may cause spider nevi or superficial telangiectasia. W. B. Bean reviews this subject in detail in *Medicine* (**24**:243, 1945). If this were true, the administration of large amounts of diethylstilbestrol to the pregnant woman might have such an effect on her offspring.